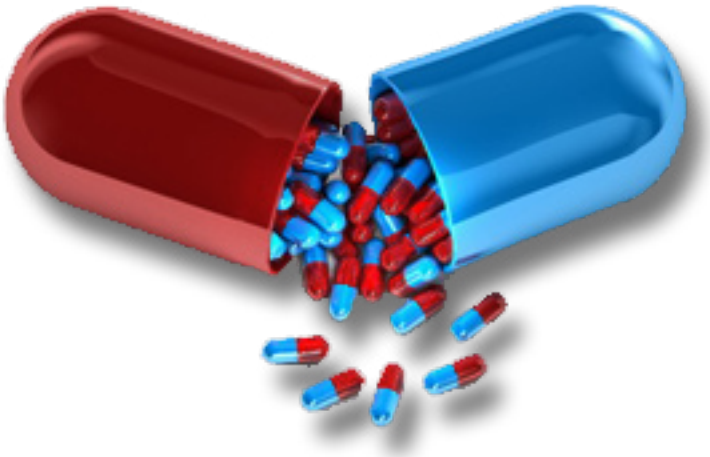
FOOD DRUGS

ADDITIVES, PRESERVATIVES, COLORS, SWEETENERS & PPCPs IN OUR FOOD & WATER



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PROLEGOMENON FORWARD

PREFACE

EXORDIUM

Diet may be the largest controllable component of our collective paths through life. One of the few aspects of life that we can each regulate to a great degree and we're learning now that diet may be significantly more important than even genetics. In fact, it's thought that your diet can alter your genes and it's believed that your diet can also transform or reprogram your children's genes. So there's more truth to "*you are what you eat*" than might initially meet the eye.

Food Drugs consumed in infinitesimally minute amounts with regularity and over decades, even those approved by the FDA and USDA as you'll soon see, will invariably cause suffering as a result of diseases and disorders directly related to that consumption. Regularly eating obesogenic, mutagenic, carcinogenic, foetotoxic, neurotoxic and endocrine disrupting chemicals has consequences and they aren't good. Moreover, eating them in combination—the different bisphenol analogues in canned sodas, the BHA and BHT in processed food, the polysorbates and parabens, tartrazine (Yellow 5) and sucralose—creates a constant daily mix of chemicals in the human body whose full effects we don't know now and won't understand for decades.

Trans Fats are a very current and perfect example, among many, of a food drug thought to be not just safe, but healthy, that is now known to cause very serious heart problems. Trans Fats are being 'voluntarily' phased out, sort of, by 2018, because they cause not just very serious heart problems, they can also cause neurological disorders and they contribute to a number of additional human diseases. Trans Fats very recently lost their "Generally Regarded As Safe (GRAS)" status and are now known to be dangerous to human health. Yet not only have we been eating them for decades, we were told they were even healthier than the real thing through the many years during which the public was effectively sold on margarine. This food additive was pushed on the public with very clever marketing campaigns, especially during the 1960s and 70s. They sold us heavily on

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trans fats and now, decades later, they're telling us they're so deadly that their GRAS status has been revoked and they're being phased out. How much damage has already been done to the human population? How many millions of innocent heart attacks are related to Trans Fats?

You'll never connect the illness(s) or disorder(s) to the drugs that were in the food you've been eating each day. Making that connection is as yet impossible except in very rare cases.

These man-made food chemicals have been manufactured in such prodigious amounts that they now irreversibly pollute the earth. Billions of tons that include their 100s of metabolites and breakdown products, many of which are still as yet unknown and undiscovered themselves, may persist in the earths environment for centuries.

They're in our rivers, our streams, our oceans, the air we breathe, the dust we're surrounded by daily, the soil and sand our children play in and these chemicals are in our food. Food drugs have become a major global ecological pollution problem—the peer review is filled with reports that spell this out clearly, and they're included here. Food drugs are ecologically ubiquitous and approaching nightmarish quantities.

Referring to Food Drugs as "*food additives*," or "*food colorings*," or "*artificial sweeteners*" is nothing less than a carefully managed media maintained misnomer and equally if not more so, a very serious insult to our collective intellect. These are drugs.

You're about to read numerous very uncomfortable facts, for example, the fact that even consuming one canned soda daily can predispose both you and your unborn children to atherosclerosis and other debilitating disorders. This is verified by not one outlier but by a number of peer reviewed reports and studies. Transgenerational food drug effects are deadly.

We're in the very infancy of understanding the complex behavior of the 100s of plant phenols, phytonutrients, flavonoids and other constituents of various plants and we're years away from fully exposing their cellular mechanics— we know even less about most Food Drugs. This lack of knowledge includes everything associated with diet—vitamins, minerals, micronutrients, artificial preservatives, artificial colors, nitrates and nitrites, excipients, intense sweeteners and non-nutritive sweeteners and many other food-related chemicals—their short and long-term interactions within the human species are still largely unknown.

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Some of these food drugs possess extraordinary healing properties, they're drugs after all. For example, tBHQ, the anti-foaming agent that came to fame as an undesirable ingredient on McDonalds' menu, is routinely administered in hospitals for severe head trauma with rather miraculous and far-reaching results. Pepsi Cola is used routinely and successfully in a specific surgical procedure. These chemicals in the food are drugs.

Every diet is, and should be, different. Variety, as the peer review informs us, of the right foods in their proper form is the essential foundation of any and every healthy diet and on this there is complete consensus. If you learn what foods to avoid and what foods your body requires and in what form, you'll be able to choose from 1000s of healthy food choices. And you should. Food variety will improve your overall health and may extend your life.

The reports collected here should go a long way in assisting towards that end although these 1600 reports are just the tip of the proverbial iceberg, a very small sample of what's available to you on the internet with simple searches. If you like this eBook, please feel free to share it.

Jeff Prager

FOOD DRUGS

Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff - Don't Eat The Food, Don't Drink The Water, Don't Buy Their Stuff -

ADDITIVES, PRESERVATIVES, FOOD COLORS, SWEETENERS & PPCPs IN OUR FOOD & WATER

And The Health Damage Associated With A Conventional Diet In More Than 1600 Peer Reviewed Reports And Studies

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This eBook was made possible through generous tax-free donations from the World Health Organization (WHO), the FDA, the USDA, Monsanto, Syngenta, Coca Cola, PepsiCo, Nestle and other major multinational chemical manufacturing company's who collectively want to protect your health so you can avoid spending your hard earned money on a lifetime of health care. In particular I want to thank Monsanto, in advance, for their tireless, decades-long, multibillion dollar effort at producing organic fruits and vegetables and organic pesticides—to clean up our earths environment. An ecosystem they and others have usurped, ravaged and despoiled for more than a century.

Thank you, all.

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The Oligopoly of Academic Publishers in the Digital Era

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Abstract

The consolidation of the scientific publishing industry has been the topic of much debate within and outside the scientific community, especially in relation to major publishers' high profit margins. However, the share of scientific output published in the journals of these major publishers, as well as its evolution over time and across various disciplines, has not yet been analyzed. This paper provides such analysis, based on 45 million documents indexed in the Web of Science over the period 1973-2013. It shows that in both natural and medical sciences (NMS) and social sciences and humanities (SSH), Reed-Elsevier, Wiley-Blackwell, Springer, and Taylor & Francis increased their share of the published output, especially since the advent of the digital era (mid-1990s). Combined, the top five most prolific publishers account for more than 50% of all papers published in 2013. Disciplines of the social sciences have the highest level of concentration (70% of papers from the top five publishers), while the humanities have remained relatively independent (20% from top five publishers). NMS disciplines are in between, mainly because of the strength of their scientific societies, such as the ACS in chemistry or APS in physics. The paper also examines the migration of journals between small and big publishing houses and explores the effect of publisher change on citation impact. It concludes with a discussion on the economics of scholarly publishing.

Introduction

This year (2015) marks the 350th anniversary of the creation of scientific journals. Indeed, it was in 1665 that the Journal des Sçavans and the Philosophical Transactions of the Royal Society of London were first published, in France and in England respectively. They were founded with the intent to advance scientific knowledge by building on colleagues' results and avoid duplication of results, and established both the principles of scientific priority and peer review. They changed the process of scholarly communication fundamentally, from personal correspondence through letters (which had become "too much for one man to cope with in his daily reading and correspondence") [1], society meetings, and books to a more structured and regular distribution of scientific advancements. This structured form, combined with a regular and wide dissemination, enabled systematic recording and archiving of scientific knowledge [1–4].

Since the 17th century, the importance of journals for diffusing the results of scientific research has increased considerably. After coexisting alongside correspondence, monographs and treaties—which often took several years to be published—they became, at the beginning of the 19th century, the fastest and most convenient way of disseminating new research results [5–7] and their number grew exponentially [1,8]. During the 20th century they consolidated their position as the main media for diffusing research [6], especially in the natural and medical sciences [9]. Scholarly journals also contributed to the professionalization of scientific activities by delimiting the frontier between popular science and the research front and, as a consequence, increased the level of specialization of research and the formation of disciplines. Interestingly, while the majority of periodicals emerged from scientific societies, a significant proportion were published by commercial ventures as early as in the Victorian era. At that time, these commercial publishing houses proved more efficient in diffusing them than scientific societies [10]. However, prior to World War II, most scholarly journals were still published by scientific societies [11]. Data from the mid-1990s by Tenopir and King [12] suggests an increase of commercial publishers' share of the output; by then, commercial publishers accounted for 40% of the journal output, while scientific/professional societies accounted for 25% and university presses and educational publishers for 16%. Along these lines, the UK Competition Commission measured various publishers' shares of ISI-indexed papers for the 1994–1998 period and showed that, over this period, Elsevier accounted for 20% of all papers published [13]. One could expect, however, that these numbers have changed during the shift from print to electronic publishing. Indeed, many authors have discussed the various transformations of the scholarly communication landscape brought by the digital era (see, among others, Borgman [14–15]; Kling and Callahan [16]; Tenopir & King [17]; Odlyzko [18]). However, although the digital format improved access, searchability and navigation within and between journal articles, the form of the scholarly journal was not changed by the digital revolution [16,19]. The PDF became the established format of electronic journal articles, mimicking the print format [20]. What was affected by the digital revolution is the economic aspect of academic publishing and the journal market.

The literature from the late 1990s suggests that the digital era could have had two opposite effects on the publishing industry. As stated by Mackenzie Owen [21], while some authors saw the Web as a potential solution to the serials' crisis—decreasing library budgets facing large and constant annual increases of journal subscription rates [22,23]—most authors hypothesized that it would actually make the situation worse [24] or, at least, not provide a solution [25,26]. Despite the fact that it is generally believed that the

digitalization of knowledge diffusion has led to a higher concentration of scientific literature in the hands of a few major players, no study has analyzed the evolution over time of these major publishers' share of the scientific output in the various disciplines. This paper aims at providing such analysis, based on all journals indexed in the Web of Science over the 1973–2013 period.

Methods

This paper uses Thomson Reuters' Web of Science (WoS)—including the Science Citation Index Expanded, the Social Sciences Citation Index and the Arts and Humanities Citation Index—transformed into a relational database optimized for bibliometric analysis. On the whole, 44,483,425 documents are analyzed for the 1973–2013 period, which include all document types published by various journals. In addition to indexing authors' names, addresses and cited references, which are the units of analysis typically used in bibliometric studies, the WoS indexes the name, city and country of the publisher of the journal for each issue. Using this information, which changes over time, we are thus able to assign journals and papers to a publisher and see the evolution of journal ownership. One limitation of this source of data is that it does not index all of the world's scientific periodicals but only those indexed in the WoS, which meet certain quality criteria such as peer review and which are the most cited in their respective disciplines. Hence, this analysis is not based on the entire scientific publication ecosystem but, rather, on the subset of periodicals that are most cited and most visible internationally.

The journal publishing market is a complex and dynamic system, with journals changing publishing houses and publishing houses acquiring or merging with competitors. Although these changes should be reflected in the publisher information provided for each issue, in some cases, the name of the publisher does not change immediately after a merger or an acquisition. Publishers' activities are often distributed among multiple companies under their control, and over the past 40 years, there have been many mergers and acquisitions involving entire companies or parts of them. We looked at the mergers and acquisitions history of major publishers, based on their number of papers published, in order to identify and associate the companies that came to be under their control, and conversely the companies which they eventually sold. These publishers are the American Chemical Society, American Institute of Physics, American Physical Society, Cambridge University Press, Emerald, IEEE, Institute of Physics, Karger, Nature Publishing Group, Optical Society of America, Oxford University Press, Reed-Elsevier, Royal Society of Chemistry, Sage Publications, Springer, Taylor & Francis, Thieme Publishing Group, Wiley-Blackwell, and Wolters Kluwer. For example, Reed-Elsevier bought Pergamon Press in 1991 but, in the WoS, journals remain associated with Pergamon Press until the year 2000. Hence, we assigned any journal published by Pergamon Press since 1991 to Reed-Elsevier. In the case of partial acquisitions, journals were assigned to the publisher only if at least 51% of the company was under its control. Historical merger and acquisition data up to 2006 was found in the report by Munroe [27]. The data for subsequent years was retrieved from the companies' profiles in the Lexis Nexis database, as well as in the press releases found on publishers' websites.

Results

Fig 1A presents, for Natural and Medical Sciences (NMS) and Social Sciences and Humanities (NMS), the proportion of papers published by the top five publishers that account for the largest number of papers in 2013, as well as the proportion of papers published in journals others than those of the top five publishers. Fig 1B provide numbers for the proportion of journals published by various publishers, while Fig 1C presents the publishers' share of citation received. What is striking for both domains is the drop, since the advent of the digital era in the in the mid-1990s, in the proportion of papers, journals and citations that are published/received by journals from publishers other than the five major publishers. In both NMS and SSH, Reed-Elsevier, Wiley-Blackwell, Springer, and Taylor & Francis are amongst the top five publishers with the highest number of scientific documents in 2013. While in NMS the American Chemical Society makes it to the top five (in fourth place in 2013), the fifth most prolific publisher in the SSH is Sage Publications. Hence, while all top publishers in SSH are private firms, one of the top publishers in NMS is a scientific society.

In terms of numbers of papers published, the five major publishers in NMS, accounted, in 1973, for little more than 20% of all papers published. This share increased to 30% in 1996, and to 50% in 2006, the level at which it remained until 2013 when it increased again to 53%. In this domain, three publishers account for more than 47% of all papers in 2013: Reed-Elsevier (24.1%; 1.5 fold increase since 1990), Springer (11.9%; 2.9 fold increase), and Wiley-Blackwell (11.3%; 2.2 fold increase). The American Chemical Society (3.4%; 5% decrease) and Taylor & Francis (2.9%; 4.9 fold increase) only account for a small proportion of papers. In the SSH, the concentration increased even more dramatically. Between 1973 and 1990, the five most prolific publishers combined accounted for less than 10% of the published output of the domain, with their share slightly increasing over the period. By the mid-1990s, their share grew to collectively account for 15% of papers. However, since then, this share has increased to more than 51%, meaning that, in 2013, the majority of SSH papers are published by journals that belong to five commercial publishers. Specifically, in 2013, Elsevier accounts for 16.4% of all SSH papers (4.4 fold increase since 1990), Taylor & Francis for 12.4% (16 fold increase), Wiley-Blackwell for 12.1% (3.8 fold increase), Springer for 7.1% (21.3 fold increase), and Sage Publications for 6.4% (4 fold increase). On the whole, for these two broad domains of scholarly knowledge, five publishers account for more than half of today's published journal output. Very similar trends are observed for journals and citations, although with a less pronounced concentration, especially for citations in NMS which have remained quite stable between 1973 and the late 1990s. For instance, while the top 5 publishers account for 53% (NMS) and 51% (SSH) of papers, their proportion of journals is of 53% (NMS) and 54% (SSH), and of 55% (NMS) and 54% (SSH) when it comes to citations received. This suggests that the top 5 publishers publish a higher number of papers per journal than other publishers not making the top five, and that their papers obtain, on average, a lower scientific impact.

The increase in the top publishers' share of scientific output has two main causes: 1) the creation of new journals and 2) existing journals being acquired by these publishers. Fig 2 presents, for both NMS and SSH, the number of journals over time that changed ownership from small to big publishers—that is, the four publishers with the largest share of published papers in both NMS and SSH—and, for NMS, the number of journals that moved from big to small publishing houses. Since we intend to emphasize developments of the publishing market by publisher type and not single actors, changes among small as well as among big publishers are not shown. It can be seen in both domains that, before 1997, publisher type changes were overall quite rare and the majority consisted of changes from big to small publishers in NMS. Importantly, not a single journal was found to have switched from a big to small publisher in SSH during the entire period of analysis. A first important large wave of journal acquisitions by the big publishers occurred in 1997–1998, when Taylor & Francis acquired several journals from Gordon & Breach Science Publishers, Harwood Academic Publishers, Scandinavian University Press, Carfax Publishing and Routledge. In the same period Reed-Elsevier acquired a few small publishers like Butterworth-Heinemann, Ablex Publications, JAI press, Gauthier-Villars and Expansion Scientifique Française. The next important peak occurred in 2001, and is mainly due to Reed-Elsevier continuing a series of acquisitions, including Academic Press, Churchill Livingstone, Mosby and WB Saunders. Finally, the peak of 2004 is

mainly due to the acquisition of Kluwer Academic Publishers by Springer, who had not previously been involved in substantial journal acquisition activities. Wiley-Blackwell's contribution to the four peaks in Fig 2 was steadier, with the company acquiring an average of 39 journals annually from various publishers during the 2001–2004 period.

The share of journal papers published by the five publishers differs amongst the various disciplines in NMS and SSH. Figs 3 and 4 present the evolution of the top five publishers' share of papers by discipline. Not surprisingly, chemistry has the highest level of concentration, as one of its disciplinary publishers, the ACS, made it to the top five most prolific publishers of NMS. For most disciplines, however, concentration in the top five publishers increased from between 10% and 20% in 1973 to between 42% and 57% in 2013, with a clear change of slope in the mid-1990s. Physics, on the other hand, follows a different pattern: after increasing from 20% in 1973 to 35% in 2000, it has since then remained stable and is subsequently the discipline where the top five publishers account for the lowest proportion of papers published. This lower concentration of papers in big publishers' journals is mainly due to the strength and size of physics' scientific societies, whose journals publish an important proportion of scientific papers in the field (Fig 5). In 2013 for instance, journals of the American Physical Society (APS) and of the American Institute of Physics (AIP) each account for 15% of papers, while those of the Institute of Physics (IOP) represent 8% of papers. It is also worth noting that, in physics, Reed-Elsevier's journals' share of papers also decreased over the last decade or so, from 28% of papers in 2001 to 21% in 2013. Springer, however, increased its percentage of physics papers from 3% to 11% over the same period. On the whole, the central importance of scientific societies in physics, the presence of arXiv, the central preprint server of physics, astrophysics and mathematics, as well as Open Access agreements such as SCOAP3 (http://scoap3.org/), are likely to make the field less profitable and thus less interesting for commercial publishers. In biomedical research, the share of the top five publishers almost reached 50% in 2009 (49%), but then decreased to 42% in 2013, mainly as a result of the emergence of new publishers, such as the Public Library of Science and its mega-journal PLOS ONE, which publishes more than 30,000 papers per year.

Fig 4 clearly shows that disciplines typically labelled as 'social sciences' behave differently from the arts and humanities. For each discipline within the domain of social sciences (psychology, professional fields, social sciences and social aspects of health), there is an unambiguous change in the slope in the mid-1990s: while the top five—in this case, commercial—publishers accounted for percentages between 15% and 22% of the output in 1995, these percentages increased to between 54% and 71% in 2013. The disciplines in social sciences, which includes specialties such as sociology, economics, anthropology, political sciences and urban studies, is quite striking: while the top five publishers accounted for 15% of papers in 1995, this value reached 66% in 2013. Combined, the top three commercial publishers alone—Reed-Elsevier, Taylor & Francis and Wiley-Blackwell—represent almost 50% of all papers in 2013. Psychology follows a similar pattern, with the top five publishers increasing from 17% in 1995 to 71% in 2013.

On the other hand, papers in arts and humanities are still largely dispersed amongst many smaller publishers, with the top five commercial publishers only accounting for 20% of humanities papers and 10% of arts papers in 2013, despite a small increase since the second half of the 1990s. The relatively low cost of journals in those disciplines—a consequence of their lower publication density—might explain the lower share of the major commercial publishers. Also, the transition from print to electronic—a strong argument for journals to convert to commercial publishers—has happened at a much slower pace in those disciplines as the use for recent scientific information is less pressing [28]. Moreover, these disciplines make a much more important use of books [9] and generally rely on local journals [29], all of which are factors that make it much less interesting for big publishers to buy journals or found new ones in the arts and humanities.

Fig 6 presents the changes in articles' relative citation rates for journals that have changed from small to big and big to small publishers (see Fig 1) for the 10 years before and after the transition. We focus on two four-year periods to ensure comparable environments for the publishing market and selected 1995–1998 and 2001–2004, as they were identified as important consolidation phases in Fig 1. More specifically, for NMS, those that have changed from small to big publishers increased their impact slightly following the change. However, while for the 2001–2004 cohort of journals this followed a drop in impact, impact of the 1995–1998 cohort was relatively stable before. For the journals moving from big to small publishers, there is no effect: impact remains similar prior to and after the change. In SSH, no noticeable effect can be observed: changing from a small to a big commercial publisher does not affect papers' citation rates. It is also worth mentioning that, except for journals moving from small to big publishers between 2001 and 2004, the mean impact of papers before and after remained below the world average. It suggests that, on average, journals changing publishers did not produce many high impact papers.

Discussion and Conclusion

The effect of scientific societies

On the whole, our results show that the top commercial publishers have benefited from the digital era, as it led to a dramatic increase in the share of scientific literature they published. It has also led to a greater dependence by the scientific community on these publishers. Despite the fact that the two broad domains have both experienced an increase in the concentration of papers in the hands of a few publishers reaching 50% in recent years, a clear distinction was observed between NMS and SSH. In the former group of disciplines, the size of scientific societies—which is a consequence of the size of disciplines in general—managed to keep the literature less dependent on commercial publishers. For example, scientific societies such as the ACS or the APS publish many journals in the specialties of chemistry and physics respectively, for which they successfully managed the shift from print to electronic. On the other hand, social sciences are much more fragmented: anthropology, communication, criminology, demography, economics and sociology can all be considered social sciences. Yet, there is no large scientific society that regroups researchers from these disciplines and that also publishes the various journals covering these different disciplines. There are, rather, many different associations for each discipline, which are often divided into specialities. Along these lines, topics in SSH are also more often local in scope—and thus much less international—which also lead to more decentralized—and thus smaller—scientific societies. As a consequence, these scientific societies did not have the means to adapt to the digital era and therefore were more likely to be acquired or have agreements with big commercial publishers for the publication of their journals. This is a clear shift from the traditional model of scholarly communication. As Lyman and Chodorow [25] put it:

"University presses and disciplinary associations were founded to disseminate research in the original cycle of scholarly communication. The faculty produced the work to be published; non-profit publishers organized the distribution of knowledge; the university library bought the published work at an artificially high price, as a subsidy for learned societies; and the faculty used this literature as the foundation for further research and teaching. […] However, over the past fifty years, as federal research funding has encouraged specialization, journal publishing has become commercialized, and some parts of the scientific and technical literature are now being monopolized by multinational publishing conglomerates." (p. 89)

The economics of scholarly publishing

As one might expect, the consolidation of the publishing industry led to an increase of the profits of publishers. Fig 7 presents, as an example, the evolution of Reed-Elsevier's profits over the 1991–2013 period,

for the firm taken as a whole as well as for its Scientific, Technical & Medical division. One can clearly see in Fig 7A that, between 1991 and 1997, both the profits and the profit margin increased steadily for the company as a whole. While profits more than doubled over that period—from 665M USD to 1,451M USD—profit margin also rose from 17% to 26%. Profit margins decreased, however, between 1998 and 2003, although profits remained relatively stable. Absolute profits as well as the profit margin then rose again, with the exception of the 2008–2009 period of economic crisis, resulting in profits reaching an all-time high of more than 2 billion USD in 2012 and 2013. The profit margin of the company's Scientific, Technical & Medical division is even higher (Fig 7B). Moreover, its profits increased by a factor of almost 6 throughout the period, and never dropped below 30% from one year to another. The profit margin of this division never decreased below 30% during the period observed, and steadily increased from 30.6% to 38.9% between 2006 and 2013. Similarly high profit margins were obtained in 2012 by Springer Science+Business Media (35.0%, see: http://static.springer.com/sgw/documents/1412702/application/pdf/Annual_Report_2012_01.pdf), and in 2013 and John Wiley & Sons' Scientific, Technical, Medical and Scholarly division (28.3%, see: http://www.wiley.com/legacy/about/corpnews/fy13_10kFINAL.pdf) and Taylor and Francis (35.7%, see: http://www.informa.com/Documents/Investor%20Relations/Annual%20Report%202013/Informa%20plc%20Annual%20Report%20Accounts%202013.pdf), putting them on a comparable level with Pfizer (42%), the Industrial & Commercial Bank of China (29%) and far above Hyundai Motors (10%), which comprise the most profitable drug, bank and auto companies among the top 10 biggest companies respectively, according to Forbes' Global 2000 [30]. At a total revenue of 9.4 billion US dollars in 2011 [31], the majority of which were generated by a few publishing houses, the scientific journal publishing market faces oligopolistic conditions, where big players such as Elsevier, Springer, Taylor & Francis, Wiley-Blackwell and Wolters Kluwer determine annually increasing subscription rates that make up a considerable amount of research spending, leaving academic libraries with no other choice but to cancel subscriptions [20,32,33].

Compilation by the authors based on the annual reports of Reed-Elsevier. (http://www.reedelsevier.com/investorcentre/pages/home.aspx) Numbers for the Scientific, Technical & Medical division were only available in GBP; conversion to USD was performed using historical conversion rates from http://www.oanda.com.

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ADDITIVES, PRESERVATIVES, COLORINGS, ARTIFICIAL SWEETENERS & PPCPs IN OUR FOOD & WATER • 1985 - 2016 • THE DANGERS OF A CONVENTIONAL DIET IN PEER REVIEW

Food & water additives, preservatives and colorings were a time-bomb, and this one blew up decades ago. We're just now seeing the ever-so-slow explosion, watching as unwilling participants. The result? A horror show. An early death, disorders—obesity, cancer, the loss of proper brain function—is the net result for us all. The majority of us ate these chemicals every single day. The majority of us still do. This eMagazine presents a massive collection of peer reviewed evidence to support the extraordinary harm that food additives are causing, not only to certain susceptible individuals, but to everyone that's eaten them. No one report or study of the more than 1600 reports in this volume verifies these concepts—no—it's purely and solely the totality of the evidence presented here that makes this all so uncomfortably true. And the evidence presented here is overwhelming. If you're eating a conventional diet of foods purchased at any grocers that's not 100% organic, you're eating yourself to a certain, painful and avoidable early death. Needlessly. The peer review proves it. The conventional food supply is poisoned. All of it.

~ Jeff Prager • July 2016 ~

MORE LOOPHOLE THAN LAW
The Food Additives Testing and Approval Process

Although consumers likely presume that a federal agency ensures the safety of ingredients in the food supply, in reality, this isn't the case.

First, many additives have not been thoroughly tested. And the vast majority of safety testing of food additives is done by food manufacturers (or by people hired by manufacturers), not the government or independent laboratories. Second, because of a loophole in the law, companies can declare on their own that an additive is "Generally Recognized As Safe" (GRAS), and start adding it to food without even informing the government. Such ingredients are required to be listed on labels although in some cases they appear simply as "artificial flavorings" or "artificial coloring".

The chapters on Povidone, a hospital and industrial disinfectant used since the 1950s, and Bisphenol A are examples of one of the latest ingredients to enter the food chain (Povidone) and one of the latest ingredients exiting (BPA). Povidone wasn't in food just a few years ago and I suspect, as the overwhelming supply of peer review mounts and public outcry builds, Bisphenol analogues will eventually be banned from use in food products. Maybe.

Some additives do undergo a more formal government approval process, but even that is no guarantee of safety. There are approved additives that have been shown in subsequent independent studies to harm health, and are in the "Avoid" category in Chemical Cuisine. But the FDA rarely reviews the safety of additives (including GRAS substances) once they enter the food supply.

BANNED ADDITIVES

The food and chemical industries have said for decades that all food additives are well tested and safe. This is not true. The history of food additives is riddled with additives that, after many years of use, were found to pose serious health risks and they are now banned. There are additives—drugs added to the food supply—that have been in use for 1, 2 and 3 decades or more and we're just now recognizing their harm medically, in the peer review. The moral of the story is that when someone says that all food additives are well tested and safe, they aren't. The peer review you're about to read proves this unequivocally. It proves how little we know.

Trans Fats will become the iconic historic example of a 'once-considered-safe' food ingredient that caused quiet, untold and unknown harm to millions. Considered GRAS, generally regarded as safe, for decades, that status was very recently removed and the US chemical and food manufacturing industries have been asked to voluntarily remove Trans Fats completely from their products by 2018. Conveniently, there's a loophole—there always is—if your product has less than 0.5 grams of Trans Fat per serving you can legally state on the product packaging, "Zero Trans Fats". All of us can now over-consume Trans Fats without even knowing it by eating properly marked cookies that state "No Trans Fat" but cookies that still contain a half gram of trans fat per every three cookies.

The health care costs associated with years-long regular ingestion of these artificially created food drugs are inestimable and reach into the stratosphere. A very few CEOs, politicos and major shareholders are cleaning the collective American plates. Yet we asked for it. It's what we wanted. If we didn't want these products, if we didn't keep buying them, they wouldn't keep making them.

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“The FDA’s reliance on industry studies in determining BPA’s safety must be re-evaluated **in light of clear signs industry is willing to mislead the American people on this public-health issue.**”

US Representative Bart Stupak, D-Michigan
Chairman of the House Energy and Commerce Committee’s
Oversight and Investigations Subcommittee

“Food distribution **is a global drug racket.**”

Jeff Prager
Publisher & Activist

INTRODUCTION

Humanity, you and I, were never intended to eat petroleum based chemicals. The peer review confirms that petroleum based chemicals—additives, colors, sweeteners, preservatives and excipients,—have been surreptitiously and almost covertly or silently introduced into the global food supply in steadily increasing quantities since the 1940s. Pesticide and herbicide use has grown alongside this increase and now a typical apple contains as many as 15 detectable chemicals. The tap water is contaminated with many 100s of disinfection breakdown products, some still as yet undiscovered, combined with dozens of pharmaceuticals and personal care products not all of which are filterable. Ibuprofen is almost impossible to filter effectively so we're all getting a dose with each sip, however small it may be. The environment itself, as the peer review will confirm, is contaminated with billions of tons of chemical run off, so much so that it now rains measurable quantities of cancer causing artificial sweeteners and endocrine disrupting bisophenol analogues are easily detectable in our rivers and streams. Conventionally grown food is contaminated with it all. And then chemicals are added to it. Those added chemicals, the colors, the sweeteners and the preservatives, should scare you away. This eBook may help towards that end.

CHAPTER ONE

Trans Fats & Hydrogenated Oils

As you read through this chapter remember that it wasn't until 2015 that the government agencies tasked with insuring the safety of our food finally removed GRAS status from trans fats, they won't be voluntarily removed from the food supply until 2018 and then, the loophole, as long as a food product contains less than 0.5 grams per serving, the product can be marked "Trans Fat Free" so you'll no longer even know if you're consuming trans fats.

Trans fats, or trans-unsaturated fatty acids or trans fatty acids, are types of unsaturated fats that are uncommon in nature but became commonly produced industrially from vegetable fats for use in margarine, snack food, packaged baked goods and frying fast food starting in the 1950s. Trans fat has been shown to consistently be associated, in an intake-dependent way, with increased risk of coronary heart disease, the worldwide leading cause of death.

Fats contain long hydrocarbon chains, which can either be unsaturated, i.e. have double bonds, or saturated, i.e. have no double bonds. In nature, unsaturated fatty acids generally have cis- as opposed to trans- configurations. In food production, liquid cis-unsaturated fats such as vegetable oils are hydrogenated to produce saturated fats, which have more desirable physical properties, e.g. they melt at a desirable temperature (30–40 °C). Partial hydrogenation of the unsaturated fat converts some of the cis double bonds into trans double bonds by an isomerization reaction with the catalyst used for the hydrogenation, which yields a trans fat. Although trans fats are edible, consumption of

The Peer Review

trans fats has shown to increase the risk of coronary heart disease [1,2] in part by raising levels of the lipoprotein LDL (so-called "bad cholesterol"), lowering levels of the lipoprotein HDL ("good cholesterol"), increasing triglycerides in the bloodstream and promoting systemic inflammation. Trans fats also occur naturally in a limited number of cases. Vaccenyl and conjugated linoleyl (CLA) containing trans fats occur naturally in trace amounts in meat and dairy products from ruminants. Most artificial trans fats are chemically different from natural trans fats. Two Canadian studies have shown that the natural trans fat vaccenic acid, found in beef and dairy products, could actually be beneficial compared to hydrogenated vegetable shortening, or a mixture of pork lard and soy fat, by lowering total LDL and triglyceride levels. A study by the US Department of Agriculture showed that vaccenic acid raises both HDL and LDL cholesterol, whereas industrial trans fats only raise LDL without any beneficial effect on HDL. In light of recognized evidence and scientific agreement, nutritional authorities consider all trans fats as equally harmful for health [3,4] and recommend that consumption of trans fats be reduced to trace amounts.

In 2013, the United States Food and Drug Administration (FDA) issued a preliminary determination that partially hydrogenated oils (which contain trans fats) are not "generally recognized as safe", which was expected to lead to a ban on industrially produced trans fats from the American diet. On 16 June 2015, the FDA finalized its determination that trans fats are not generally recognized as safe, and set a three-year time limit for their removal from all processed foods [5,6] with a loophole of course. Anything under 0.5 grams of trans fats per serving ...

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Some major food chains have chosen to remove or reduce trans fats in their products. In some cases these changes have been voluntary. In other cases, however, food vendors have been targeted by legal action that has generated a lot of media attention. In May 2003, BanTransFats.com Inc., a U.S. non-profit corporation, filed a lawsuit against the food manufacturer Kraft Foods in an attempt to force Kraft to remove trans fats from the Oreo cookie. The lawsuit was withdrawn when Kraft agreed to work on ways to find a substitute for the trans fat in the Oreo. In November 2006, Arby's announced that by May 2007, it would be eliminating trans fat from its French fries and reducing it in other products.

Similarly, in 2006, the Center for Science in the Public Interest sued KFC over its use of trans fats in fried foods. Concerning their class action complaint, KFC reviewed alternative oil options, saying "there are a number of factors to consider including maintaining KFC's unique taste and flavor of Colonel Sanders' Original Recipe". On 30 October 2006, KFC announced that it will replace the partially hydrogenated soybean oil it currently uses with a zero trans fat low linoleic soybean oil in all restaurants in the US by April 2007, although its biscuits will still contain trans fats. Despite the US-specific nature of the lawsuit, KFC is making changes outside of the US as well; in Canada, KFC's brand owner is switching to trans fat free Canadian canola oil by early 2007. Wendy's announced in June 2006 plans to eliminate trans fats from 6,300 restaurants in the United States and Canada, starting in August 2006. In November 2006, Taco Bell made a similar announcement, promising to remove trans fat from many of their menu items by switching to canola oil. By April 2007, 15 Taco Bell menu items were completely free of trans fat. In January 2007, McDonald's announced they will start phasing out the trans fat in their fries after years of testing and several delays. This can be partially attributed to New York's recent ban, with the company stating they would not be selling a unique oil just for New York customers but would implement a nationwide change. Chick-fil-A's menu is trans fat free as of 9 October 2007.

In response to a May 2007 lawsuit from the Center for Science in the Public Interest, Burger King announced that its 7,100 US restaurants would begin their switch to a menu containing zero grams of trans fat oil by the year 2008.

The Walt Disney Company announced that they will begin getting rid of trans fats in meals at US theme parks by the end of 2007, and will stop the inclusion of trans fats in licensed or promotional products by 2008.

Although IHOP restaurants pledged in a 2007 press release to eliminate transfat from their food, the nutrition information on the company website for the Summer/Fall 2015 Core Menu shows that they still have a considerable amount of transfat in their food, including 4.5 grams in their "mega monster cheeseburger".

The Girl Scouts of the USA announced in November 2006 that all of their cookies contain less than 0.5 g trans fats per serving, thus meeting or exceeding the FDA guidelines for the "zero trans fat" designation.

Health Canada's monitoring program, which tracks the changing amounts of TFA and SFA in fast and prepared foods shows considerable progress in TFA reduction by some industrial users while others lag behind. In many cases, SFAs are being substituted for the TFAs

The problem lies in what the trans fats are being replaced with and until we know and have had time to test the replacements for toxicity we may not be much better off. Here's the Hydrogenated Oil & Trans Fat peer review:

Manufacturing Hydrogenated Oils

WHY TRANS FATS?
How Body Fat Hurts your Brain

By Elise Brett, MD, FACE, ECNU
It's a fact: Being overweight is bad for your brain

Compared with normal weight individuals, people who are overweight in midlife have a 30 percent greater risk of developing dementia (memory loss and decreased cognitive function) such as Alzheimer's disease later in life. Not only that, but obesity is associated with smaller brain sizes and decreased cognitive function in middle-aged people.

Besides high body mass index (BMI, a measure of body fat based on an individual's height and weight), central obesity (large waist circumference) is also associated with dementia and so is type 2 diabetes, which is more common in people who are overweight or obese. People with type 2 diabetes have twice the risk for dementia and, as a group, perform worse than people without diabetes on tests of cognitive function on memory.

While it is possible that certain factors other than fat mass are at play, such as high-fat, high-calorie diets, lack of intake of certain vitamins or other nutrients and higher alcohol use, there is mounting evidence that fat itself affects the brain. Scientists used to believe that fat mass was an inactive reserve of body tissue. We now know that fat is an active endocrine organ that secretes numerous substances that have an effect on the rest of the body. These substances are called "adipocytokines," [ad'i-pō-sīt-o-kīns] and are involved in metabolism and inflammation.

Many such substances may play a role in the development of dementia, but the two with the most convincing scientific evidence are "adiponectin" [ad'i-pō-nek'tin] and "leptin." Adiponectin is involved in the regulation of energy expenditure, sugar metabolism and fat metabolism and is higher in thin individuals. Adiponectin blocks production of inflammatory "cytokines" [si-to-kins] and has been shown to have effects on protecting the brain. Rats who do not make adiponectin have been shown to be more susceptible to strokes.

Leptin is involved in the long-term control of body weight. New evidence shows that leptin also probably plays a role in memory, nerve growth, nerve protection and brain structure. Leptin improves nerve survival and slows nerve damage in animals with dementia. Giving leptin directly to mice brains improves their memory. People with obesity have high leptin levels, but also have leptin "resistance," so the normally protective actions of leptin are not as effective. It has also been shown that in obese people, leptin may not reach the brain in adequate levels.

Thus, there is increasing evidence for a direct causal role of fat mass in the development of dementia. As our country's population lives longer and simultaneously becomes fatter, obesity-related dementia may present a substantial public health problem. Treatments for dementia are only minimally effective, yet another reason to try to achieve and maintain healthy weight in midlife.

Dr. Elise M. Brettis Associate Clinical Professor at the Icahn School of Medicine at Mount Sinai and is in private practice specializing in Endocrinology and Metabolic Support in New York City. Dr. Brett completed her undergraduate education at the University of Michigan, received her medical degree from Mount Sinai School of Medicine, and completed her internal medicine residency and fellowship in endocrinology and metabolism at The Mount Sinai Hospital. She is board certified in endocrinology and metabolism.

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Effect of a trans fatty acid-enriched diet on biochemical and inflammatory parameters in Wistar rats

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Abstract

PURPOSE:

Recent data regarding trans fatty acids (TFAs) have implicated these lipids as particularly deleterious to human health, causing systemic inflammation, endothelial dysfunction and possibly inflammation in the central nervous system (CNS). We aimed to clarify the impact of partially hydrogenated soybean oil (PHSO) with different TFA concentrations on cerebrospinal fluid (CSF), serum and hepatic parameters in adult Wistar rats.

METHODS:

Wistar rats (n = 15/group) were fed either a normolipidic diet or a hyperlipidic diet for 90 days. The normolipidic and hyperlipidic diets had the same ingredients except for fat compositions, concentrations and calories. We used lard in the cis fatty acid group and PHSO in the trans fatty acid group. The intervention groups were as follows: (1) low lard (LL), (2) high lard (HL), (3) low partially hydrogenated soybean oil (LPHSO) and (4) high partially hydrogenated soybean oil (HPHSO). Body weight, lipid profiles and the inflammatory responses in the CSF, serum and liver tissue were analyzed.

RESULTS:

Surprisingly, with the PHSO diet we observed a worse metabolic response that was associated with oxidative stress in hepatic tissue as well as impaired serum and CSF fluid parameters at both PHSO concentrations. In many analyses, there were no significant differences between the LPHSO and HPHSO diets.

CONCLUSIONS:

Dietary supplementation with PHSO impaired inflammatory parameters in CSF and blood, induced insulin resistance, altered lipid profiles and caused hepatic damage. Overall, these findings suggest that fat composition is more important than the quantity of fat consumed in terms of cis and trans fatty acid diets.

http://www.ncbi.nlm.nih.gov/pubmed/26754301

> “Dietary supplementation with partially hydrogenated soybean oil impaired inflammatory parameters in cerebrospinal fluid and blood, induced insulin resistance, altered lipid profiles and caused hepatic damage.”

“To minimise the intake of industrially produced trans fat (I-TF) and thereby decrease the risk of coronary heart disease (CHD), nearly all European countries rely on food producers to voluntarily reduce the Industrial Produced Trans Fat content in food. The findings suggest that voluntary reduction of I-TF in foods with high amounts is an ineffective strategy in several European countries.

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Artificial trans fat in popular foods in 2012 and in 2014: a market basket investigation in six European countries

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Abstract

OBJECTIVE

To minimise the intake of industrially produced trans fat (I-TF) and thereby decrease the risk of coronary heart disease (CHD), nearly all European countries rely on food producers to voluntarily reduce the I-TF content in food. The objective of this study was to monitor the change in presence of I-TF in biscuits/cakes/wafers in six countries in South-eastern Europe from 2012 to 2014, including two members of the European Union (Slovenia and Croatia).

DESIGN

Three large supermarkets were visited in each of the six capitals in 2012. Pre-packaged biscuits/cakes/wafers were bought if the products contained more than 15 g of total fat per 100 g of product and if partially hydrogenated oil or a similar term was disclosed at the beginning of the ingredients list. These same supermarkets were revisited in 2014 and the same collection procedure was followed. All foods were subsequently analysed for total fat and trans fat in the same laboratory.

RESULTS

The number of packages bought in the six countries taken together was 266 in 2012 and 643 in 2014. Some were identical, and therefore only 226 were analysed in 2012 and 434 in 2014. Packages with less than 2% of fat from I-TF went up from 69 to 235, while products with more than 2% (illegal in Denmark) doubled from an average of 33 to an average of 68 products for the six countries, with considerable variation across countries. The per cent of I-TF in total fat decreased slightly, from a mean (SD) of 22 (13) in 2012 to 18 (9) in 2014.

CONCLUSIONS

The findings suggest that voluntary reduction of I-TF in foods with high amounts is an ineffective strategy in several European countries. Alternative strategies both within and outside the European Union are necessary to protect all subgroups of the populations against an increased risk of CHD.

Full text, graphs, charts and 26 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4800119/

“The benefits of choosing polyunsaturated fat over saturated fat seem a little less certain than we thought. While we wait for further clarification, we should continue to eat (and to advise others to eat) more fish, fruits, vegetables, and whole grains. We should avoid salt, sugar, industrial trans fats, and avoid over eating.”

BMJ • April 2016

Dietary fats: a new look at old data challenges established wisdom

By J. Lennert Veerman, senior lecturer
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Abstract

It is widely accepted that diets rich in polyunsaturated fats protect against heart disease. Recently, the Global Burden of Disease team reported that each year insufficient intake of omega-6 polyunsaturated fats, the most common subgroup of polyunsaturated fats, results in over 700 000 deaths from coronary heart disease.1 Or does it? A linked study by Ramsden and colleagues (doi:10.1136/bmj.i1246) adds to the doubts around the health benefits of replacing saturated fat with polyunsaturated fats.

The benefits of choosing polyunsaturated fat over saturated fat seem a little less certain than we thought. While we wait for further clarification, we should continue to eat (and to advise others to eat) more fish, fruits, vegetables, and whole grains. We should avoid salt, sugar, industrial trans fats, and avoid over eating.

Full text with 14 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4829658/

“Monounsaturated fatty acids (MUFA) have been newly suggested to be involved in regulating fat oxidation, energy metabolism, appetite sensations, weight maintenance, and cholesterol metabolism. These favorable effects might implicate MUFA as the preferable choice to substitute for other fatty acids, especially given the declaration of its safety for up to 20% of total energy.”

Lipids • May 2016

Current Evidence Supporting the Link Between Dietary Fatty Acids and Cardiovascular Disease

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Abstract

Lack of consensus exists pertaining to the scientific evidence regarding effects of various dietary fatty acids on cardiovascular disease (CVD) risk. The objective of this article is to review current evidence concerning cardiovascular health effects of the main dietary fatty acid types; namely, trans (TFA), saturated (SFA), polyunsaturated (PUFA; n-3 PUFA and n-6 PUFA), and monounsaturated fatty acids (MUFA). Accumulating evidence shows negative health impacts of TFA and SFA; both may increase CVD risk. Policies have been proposed to reduce TFA and SFA consumption to less than 1 and 7 % of energy intake, respectively. Cardiovascular health might be promoted by replacing SFA and TFA with n-6 PUFA, n-3 PUFA, or MUFA; however, the optimal amount of PUFA or MUFA that can be used to replace SFA and TFA has not been defined yet. Evidence suggests of the potential importance of restricting n-6 PUFA up to 10 % of energy and obtaining an n-6/n-3 ratio as close as possible to unity, along with a particular emphasis on consuming adequate amounts of essential fatty acids. The latest evidence shows cardioprotective effects of MUFA-rich diets, especially when MUFA are supplemented with essential fatty acids; namely, docosahexaenoic acid. MUFA has been newly suggested to be involved in regulating fat oxidation, energy metabolism, appetite sensations, weight maintenance, and cholesterol metabolism. These favorable effects might implicate MUFA as the preferable choice to substitute for other fatty acids, especially given the declaration of its safety for up to 20 % of total energy.

http://www.ncbi.nlm.nih.gov/pubmed/26719191

“These results support our hypothesis that consumption of a diet high in trans-fatty acids induces higher rates of obesity, Insulin Resistance and hepatic steatosis ...”

Molecules • May 2016

Trans-Fatty Acids Aggravate Obesity, Insulin Resistance and Hepatic Steatosis in C57BL/6 Mice, Possibly by Suppressing the IRS1 Dependent Pathway

Author information

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Abstract

Trans-fatty acid consumption has been reported as a risk factor for metabolic disorders and targeted organ damages. Nonetheless, little is known about the roles and mechanisms of trans-fatty acids in obesity, insulin resistance (IR) and hepatic steatosis. Adult C57BL/6 male mice were fed with four different diets for 20 weeks: normal diet (ND), high fat diet (HFD), low trans-fatty acids diet (LTD) and high trans-fatty acid diet (HTD). The diet-induced metabolic disorders were assessed by evaluating body weight, glucose tolerance test, hepatic steatosis and plasma lipid profiles post 20-week diet. Histological (H&E, Oil-Red-O) staining and western blot analysis were employed to assess liver steatosis and potential signaling pathways. After 20-weeks of diet, the body weights of the four groups were 29.61 ± 1.89 g (ND), 39.04 ± 4.27 g (HFD), 34.09 ± 2.62 g (LTD) and 43.78 ± 4.27 g (HTD) ($p < 0.05$), respectively. HFD intake significantly impaired glucose tolerance, which was impaired further in the mice consuming the HTD diet. The effect was further exacerbated by HTD diet. Moreover, the HTD group exhibited significantly more severe liver steatosis compared with HFD group possibly through regulating adipose triglyceride lipase. The group consuming the HTD also exhibited significantly reduced levels of IRS1, phosphor-PKC and phosphor-AKT. These results support our hypothesis that consumption of a diet high in trans-fatty acids induces higher rates of obesity, IR and hepatic steatosis in male C57BL/6 mice, possibly by suppressing the IRS1dependent pathway.

Full text link, PDF link, photos, graphs, charts and 36 references

http://www.mdpi.com/1420-3049/21/6/705

Expert Reviews In Cardiovascular Therapy • June 2016

Trans-fatty acids and cardiovascular risk: does origin matter?

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Abstract

“Several studies have aimed to unravel the contribution of different types of dietary fatty acids to human health and disease. **Investigations have consistently shown that high consumption of industrially produced trans-fatty acids from partially hydrogenated vegetable oils is harmful to human health, in particular cardiovascular health.** Therefore, the U.S. Food and Drug Administration announced that partially hydrogenated oils are no longer ‘generally recognized as safe’, and trans-fatty acids are not permitted in the U.S. food supply. On the other hand, recent studies analyzing the association between circulating trans-fatty acids and disease have revealed that **some ruminant-specific trans-fatty acids are associated with a reduction in incidence of disease.** In this special report, we highlight recent findings and point out perspectives for future studies on this topic.”

http://www.ncbi.nlm.nih.gov/pubmed/27292099

“Trans Fatty Acid content in Spain is low and has significantly fallen since 2010.”

Gaceta Sanitaria • June 2016

Trans-fatty acid content of food products in Spain in 2015

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Abstract

OBJECTIVE

To ascertain the content of trans-fatty acids (TFA) in food products in Spain in 2015 and assess trends in TFA content since 2010.

METHODS

We analysed the fat content of 277 food products purchased in Spanish supermarkets in 2015 and calculated both the total fat and TFA content and the proportion of TFA to total fats. The results obtained in 2015 were compared to those yielded by a similar study in 2010.

RESULTS

In 2015, the majority of food products studied had a TFA content of less than 0.2g/100g product, and a TFA/total fat ratio of less than 2%. No significant increases were found compared to 2010. Food groups with a higher TFA content were dairy products of possible natural origin.

CONCLUSIONS

TFA content in Spain is low and has significantly fallen since 2010.

Full text, charts and 15 references

http://www.gacetasanitaria.org/en/linkresolver/trans-fatty-acid-content-of-food/S0213-9111(16)30052-8/

“This study will contribute to important knowledge on how the applied cooking methods can change the nutritional quality and safety of foods, namely of chicken nuggets, and can be very useful for dietary recommendations and nutritional assessment.”

Food Function • June 2016

The impact of cooking methods on the nutritional quality and safety of chicken breaded nuggets

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Abstract

The impact of cooking methods (industrial pre-frying, deep-fat frying and baking) on the nutritional quality and safety of chicken breaded nugget samples from supermarket and commercial brands was evaluated. The changes in the quality characteristics (nutritional composition, fatty acids profile, cholesterol and salt) of the fried food and frying oil, after ten consecutive frying operations, were evaluated. The total fat content of nuggets varied between 10.9 and 22.7 g per 100 g of edible portion and the salt content ranged from 0.873 to 1.63 g per 100 g. Taking into account one portion of nuggets, the daily intake of salt can reach 49%, which can have a significant impact on the health of those who regularly consume this type of food, especially considering the prevalence of hypertension around the world. The analysed chicken breaded nuggets are rich in unsaturated fatty acids, which have been related with potential health benefits, namely regarding cardiovascular diseases. The cholesterol content of baked samples was two times higher when compared with the fried ones. The trans fatty acids and polar compounds contents of the frying oil used for frying significantly increased, but the values were still away from the maximum recommended by legal entities for its rejection. From a nutritional point of view, it is possible to conclude that the applied cooking methods can significantly influence the nutritional quality and safety of the analysed chicken breaded nuggets. This study will contribute to important knowledge on how the applied cooking methods can change the nutritional quality and safety of foods, namely of chicken nuggets, and can be very useful for dietary recommendations and nutritional assessment.

http://www.ncbi.nlm.nih.gov/pubmed/27213579

“Trans fatty acids in Western diets increase health risks, and have been associated with the risk of depression.”

Nutritional Research • June 2016

Trans fatty acid intake is related to emotional affect in the Adventist Health Study-2

Author information

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Abstract

Trans fatty acids in Western diets increase health risks, and have been associated with the risk of depression. We hypothesized that intakes of trans fatty acids (primarily from margarines and baked goods) were inversely associated with positive affect and positively associated with negative affect in a longitudinal study. Church attendees residing in North America completed a food frequency questionnaire in 2002-6 as part of the Adventist Health Study-2. A subset in which we excluded participants with established cardiovascular disease (n=8,771) completed the Positive and Negative Affect Schedule (PANAS) in 2006-7. The associations between dietary intakes of fatty acids to positive and negative affect were tested with linear regression analysis controlling for age, gender, ethnicity, education, body mass index, exercise, sleep, sleep squared, Mediterranean diet, total energy intake and alcohol. Intakes of trans fatty acids were inversely associated with positive affect (ß=-0.06, B=-0.27 [95% CI -0.37, -0.17], p<.001) and positively associated with negative affect (ß=0.05, B=0.21 [95% CI 0.11, 0.31], p<.001). In comparison, we found no association between n-3 polyunsatured fatty acids (PUFA) intakes with affect. The n-6:n-3 PUFA ratio was inversely associated with positive affect (ß=-0.03, B=-0.34 [95% CI -0.58, -0.10], p=0.006). The findings suggest that a lower dietary trans fatty acid intake has beneficial effects on emotional affect while the n-6: n-3 ratio is detrimental to positive affect.

http://www.ncbi.nlm.nih.gov/pubmed/27188896

“A high consumption of trans fatty acids (TFAs) is associated with an increased risk of cardiovascular diseases.”

Epigenetics • June 2016

Variations in HDL-carried miR-223 and miR-135a concentrations after consumption of dietary trans fat are associated with changes in blood lipid and inflammatory markers in healthy men - an exploratory study

Author information

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Abstract

A high consumption of trans fatty acids (TFAs) is associated with an increased risk of cardiovascular diseases (CVDs). High-density lipoproteins (HDLs) have many cardioprotective properties and transport functional microRNAs (miRNAs) to recipient cells. We hypothesized that dietary TFAs modify the HDL-carried miRNA profile, therefore modulating its cardioprotective properties. We assessed whether consumption of dietary TFAs modifies HDL-carried miR-223-3p and miR-135a-3p concentration and the inter-relationship between diet-induced changes in HDL-carried miRNA concentration and CVD risk markers. In a double blind, randomized, crossover, controlled study, 9 men were fed each of 3 experimental isoenergetic diets: 1) High in industrial TFA (iTFA; 3.7% energy); 2) High in TFA from ruminants (rTFA; 3.7% energy); 3) Low in TFA (control; 0.8% energy) for 4 weeks each. HDLs were isolated by ultracentrifugation and miRNAs were quantified by RT-qPCR. Variations in HDL-miR-223-3p concentration were negatively correlated with variations in HDL-cholesterol after the iTFA diet (rs = 0.82; P = 0.007), and positively correlated with variations in C-reactive protein concentration after the rTFA diet (rs = 0.75; P = 0.020). Variations in HDL-miR-135a-3p concentration were positively correlated with variations in total triglyceride (TG) concentration following the iTFA diet (rs = -0.82; P = 0.007), and with variations in low-density lipoprotein (LDL)-TG concentration following the rTFA diet (rs = 0.83; P = 0.005), compared to the control diet. However, the consumption of dietary TFAs has no significant unidirectional impact on HDL-carried miR-223-3p and miR-135a-3p concentrations. Our results suggest that the variability in the HDL-carried miRNAs response to TFA intake, by being associated with variations in CVD risk factors, might reflect physiological changes in HDL functions.

http://www.ncbi.nlm.nih.gov/pubmed/27099924

“... chronic consumption of trans fat is able to enhance impulsiveness and reactivity to novelty, **facilitating hyperactive behaviors.**”

Physiology & Behavior • February 2015

Chronic consumption of trans fat can facilitate the development of hyperactive behavior in rats

Author information

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Abstract

In recent decades, the increased consumption of processed foods, which are rich in hydrogenated vegetable fat (HVF), has led to a decreased consumption of fish and oilseed, rich in omega-3 fatty acids. This eating habit provides an increased intake of trans fatty acids (TFA), which may be related to neuropsychiatric conditions, including inattention and hyperactivity. In this study, we evaluated the potential connection between prolonged trans fat consumption and development of hyperactivity-like symptoms in rats using different behavioral paradigms. Trans fat intake for 10 months (Experiment 1), as well as during pregnancy and lactation across two sequential generations of rats, (Experiment 4) induced active coping in the forced swimming task (FST). In addition, HVF supplementation was associated with increased locomotion before and after amphetamine (AMPH) administration (Experiment 2). Similarly, HVF supplementation during pregnancy and lactation were associated with increased locomotion in both young and adult rats (Experiment 3). Furthermore, trans fat intake across two sequential generations increased locomotor and exploratory activities following stressors (Experiment 4). From these results, we suggest that chronic consumption of trans fat is able to enhance impulsiveness and reactivity to novelty, facilitating hyperactive behaviors.

http://www.ncbi.nlm.nih.gov/pubmed/25433314

“These findings reinforce that prolonged consumption of trans fat allows trans fatty acid incorporation in the cortex, **facilitating hyperactive behavior, oxidative damages and molecular changes. Our study is a warning about cross-generational consumption of processed food**, since high trans fat may facilitate the development of neuropsychiatric conditions, including bipolar disorder.”

Neuroscience • February 2015

Cross-generational trans fat intake facilitates mania-like behavior: oxidative and molecular markers in brain cortex

Author information

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Abstract

Since that fast food consumption have raised concerns about people’s health, we evaluated the influence of trans fat consumption on behavioral, biochemical and molecular changes in the brain-cortex of second generation rats exposed to a model of mania. Two successive generations of female rats were supplemented with soybean oil (SO, rich in n-6 FA, control group), fish oil (FO, rich in n-3 FA) and hydrogenated vegetable fat (HVF, rich in trans FA) from pregnancy, lactation to adulthood, when male rats from 2nd generation received amphetamine (AMPH-4 mg/kg-i.p., once a day, for 14 days) treatment. AMPH increased locomotor index in all animals, which was higher in the HVF group. While the FO group showed increased n-3 polyunsaturated fatty acid (PUFA) incorporation and reduced n-6/n-3 PUFA ratio, HVF allowed trans fatty acid (TFA) incorporation and increased n-6/n-3 PUFA ratio in the brain-cortex. In fact, the FO group showed minor AMPH-induced hyperactivity, decreased reactive species (RS) generation per se, causing no changes in protein carbonyl (PC) levels and dopamine transporter (DAT). FO supplementation showed molecular changes, since proBDNF was increased per se and reduced by AMPH, decreasing the brain-derived neurotrophic factor (BDNF) level following drug treatment. Conversely, HVF was related to increased hyperactivity, higher PC level per se and higher AMPH-induced PC level, reflecting on DAT, whose levels were decreased per se as well as in AMPH-treated groups. In addition, while HVF increased BDNF-mRNA per se, AMPH reduced this value, acting on BDNF, whose level was lower in the same AMPH-treated experimental group. ProBDNF level was influenced by HVF supplementation, but it was not sufficient to modify BDNF level. These findings reinforce that prolonged consumption of trans fat allows TFA incorporation in the cortex, facilitating hyperactive behavior, oxidative damages and molecular changes. Our study is a warning about cross-generational consumption of processed food, since high trans fat may facilitate the development of neuropsychiatric conditions, including bipolar disorder (BD).

http://www.ncbi.nlm.nih.gov/pubmed/25499313

“The strongest inflammatory effect was induced by margarine, which contains the highest level of trans-fatty acids, or 2% of total fat. Increased trans-fatty acids consumption was associated with increased histological aspects of **atherosclerotic lesions** in a dose-dependent manner. Process-induced Trans Fatty Acids cause changes including **proatherogenic plasma lipid markers, heart fatty acid profiles, and coronary artery histology** ...”

Journal Of The American College Of Nutrition • March 2015

Consumption of Oxidized and Partially Hydrogenated Oils Differentially Induces Trans-Fatty Acids Incorporation in Rats’ Heart and Dyslipidemia

Author information

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Abstract

OBJECTIVES

A direct effect of process-induced trans-fatty acids (TFAs) on nonalcoholic fatty liver disease (NAFLD) as a cardiovascular disease (CVD) risk factor has previously been shown. We hypothesized that TFAs directly induced CVD. This article describes an investigation of the association between TFAs, provided by the consumption of oxidized soybean oil and margarine, and plasma lipid profiles, coronary artery lesions, and coronary fatty acids distribution in rats. Male rats were fed a standard chow or high-fat diet containing different TFA levels ranging from <1%, <2%, and >2% of total fat in fresh soybean oil, oxidized soybean oil, and margarine, respectively, for 4 weeks.

RESULTS

The results indicated that the high-fat diets differently changed the plasma lipid profiles by significantlt increasing triglycerides, total cholesterol, low-density lipoprotein cholesterol, and the ratio of low-density to high-density lipoprotein cholesterol compared to control rats. Compared to fresh soybean oil, oxidized oil further increased plasma lipid markers. The strongest inflammatory effect was induced by margarine, which contains the highest level of TFAs, or 2% of total fat. Total TFAs in the heart of the margarine-fed group were increased by 4.7 regarding to control and by 2.17 and 2.6 relative to groups receiving oxidized and fresh oil, respectively. Increased TFAs consumption was associated with increased histological aspects of atherosclerotic lesions in a dose-dependent manner.

CONCLUSION

In conclusion, process-induced TFAs cause changes including proatherogenic plasma lipid markers, heart fatty acid profiles, and coronary artery histology depending on the TFA level in the supplemented fat and therefore on the type of technological process used.

http://www.ncbi.nlm.nih.gov/pubmed/25794039

“the Hydrogenated Vegetable Fat group showed **increased skin thickness and reactive species generation, with decreased skin antioxidant defenses.** Once incorporated to skin, Trans Fatty Acids make it more susceptible to developing **Ultra Violet Radiation-induced [sun induced] disorders.**”

Organic Photochemistry And Photobiology • March 2015

Influence of trans fat on skin damage in first-generation rats exposed to UV radiation

Author information

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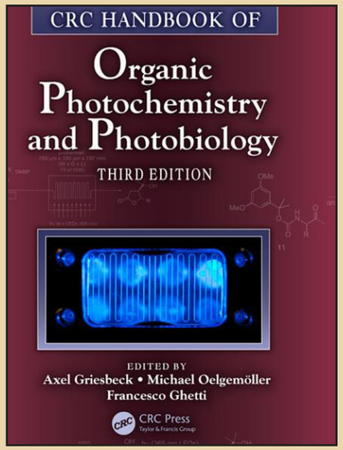
Abstract

The influence of trans fatty acids (TFA) on lipid profile, oxidative damage and mitochondrial function in the skin of rats exposed to ultraviolet radiation (UVR) was assessed. The first-generation offspring of female Wistar rats supplemented from pregnancy with either soybean oil (C-SO, rich in n-6 FA; control group) or hydrogenated vegetable fat (HVF, rich in TFA) were continued with the same supplements until adulthood, when half of each group was exposed to UVR for 12 weeks. The HVF group showed higher TFA cutaneous incorporation, increased protein carbonyl (PC) levels, decreased functionality of mitochondrial enzymes and antioxidant defenses of the skin. After UVR, the HVF group showed increased skin thickness and reactive species (RS) generation, with decreased skin antioxidant defenses. RS generation was positively correlated with skin thickness, wrinkles and PC levels. Once incorporated to skin, TFA make it more susceptible to developing UVR-induced disorders.



http://www.ncbi.nlm.nih.gov/pubmed/25600099

Hippocampus • May 2015

Cross-generational trans fat intake modifies BDNF mRNA in the hippocampus: Impact on memory loss in a mania animal model

Author information

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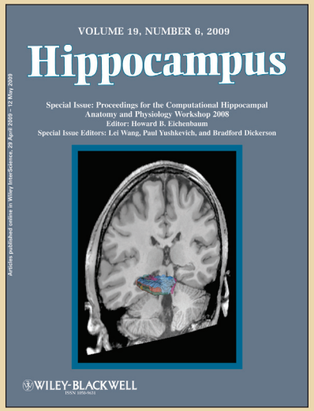
> “... chronic consumption of trans fats over two generations can facilitate the development of **mania-like behavior**, so leading to **memory impairment** and emotionality, which are related to **neuropsychiatric conditions.**”

Abstract

Recently, we have described the influence of dietary fatty acids (FA) on mania-like behavior of first generation animals. Here, two sequential generations of female rats were supplemented with soybean oil (SO, rich in n-6 FA, control group), fish oil (FO, rich in n-3 FA) and hydrogenated vegetable fat (HVF, rich in trans FA) from pregnancy and during lactation. In adulthood, half of each group was exposed to an amphetamine (AMPH)-induced mania animal model for behavioral, biochemical and molecular assessments. FO supplementation was associated with lower reactive species (RS) generation and protein carbonyl (PC) levels and increased dopamine transporter (DAT) levels, while HVF increased RS and PC levels, thus decreasing catalase (CAT) activity and DAT levels in hippocampus after AMPH treatment. AMPH impaired short- (1 h) and long- (24 h) term memory in the HVF group. AMPH exposure was able to reduce hippocampal BDNF- mRNA expression, which was increased in FO. While HVF was related to higher trans FA (TFA) incorporation in hippocampus, FO was associated with increased percentage of n-3 polyunsaturated FA (PUFA) together with lower n-6/n-3 PUFA ratio. Interestingly, our data showed a positive correlation between brain-derived neurotrophic factor (BDNF) mRNA and short- and long-term memory ($r(2) = 0.53$; $P = 0.000$/$r(2) = 0.32$; $P = 0.011$, respectively), as well as a negative correlation between PC and DAT levels ($r(2) = 0.23$; $P = 0.015$). Our findings confirm that provision of n-3 or TFA during development over two generations is able to change the neuronal membrane lipid composition, protecting or impairing the hippocampus, respectively, thus affecting neurothrophic factor expression such as BDNF mRNA. In this context, chronic consumption of trans fats over two generations can facilitate the development of mania-like behavior, so leading to memory impairment and emotionality, which are related to neuropsychiatric conditions.



http://www.ncbi.nlm.nih.gov/pubmed/25394793

“There appears to be a significant association of Western dietary pattern with the **increased risk of coronary heart disease, strokes, and associated risk factors** among adults in the Middle East and North Africa region. Conversely, increased adherence to Mediterranean and/or dietary approach to stop hypertension dietary patterns or their individual food components is associated with a decreased risk of coronary heart disease and the associated risk factors.”

Food Nutrition Research • June 2015

Association between dietary pattern and risk of cardiovascular disease among adults in the Middle East and North Africa region: a systematic review

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Abstract

OBJECTIVE

This paper reviews the evidence related to the association of dietary pattern with coronary heart disease (CHD), strokes, and the associated risk factors among adults in the Middle East and North Africa (MENA) region.

RESULTS

The search identified 15 studies. The available data in the MENA region showed that Western dietary pattern has been predominant among adults with fewer adherences to the traditional diet, such as the Mediterranean diet. The Western dietary pattern was found to be associated with an increased risk of dyslipidaemia, diabetes, metabolic syndrome (MetS), body mass index (BMI), and hypertension. The Mediterranean diet, labelled in two studies as ‘the traditional Lebanese diet’, was negatively associated with BMI, waist circumference (WC), and the risk of diabetes, while one study found no association between the Mediterranean diet and MetS. Two randomised controlled trials conducted in Iran demonstrated the effect of the dietary approach to stop hypertension (DASH) in reducing metabolic risk among patients with diabetes and MetS. Likewise, the consumption of dairy products was associated with decreased blood pressure and WC, while the intake of whole grains was associated with reduced WC. In addition, the high consumption of black tea was found to be associated with decreased serum lipids. The intake of fish, vegetable oils, and tea had a protective effect on CHD, whereas the intake of full-fat yoghurt and hydrogenated fats was associated with an increased risk of CHD.

CONCLUSION

There appears to be a significant association of Western dietary pattern with the increased risk of CHD, strokes, and associated risk factors among adults in the MENA region. Conversely, increased adherence to Mediterranean and/or DASH dietary patterns or their individual food components is associated with a decreased risk of CHD and the associated risk factors. Therefore, increasing awareness of the high burden of CHD and the associated risk factors is crucial, as well as the need for nutrition education programs to improve the knowledge among the MENA population regarding healthy diets and diet-related diseases.

Full Report with Graphs, Charts and 45 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4472555/

Life Science • July 2015

Trans-fat supplementation over two generations of rats exacerbates behavioral and biochemical damages in a model of mania: Co-treatment with lithium

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Abstract

AIMS

We investigated whether trans-fat supplemented over two generations of rats could alter neuronal membranes and influence mania-like behaviors, as well as the effects of lithium (Li).

MAIN METHODS

Two generations of female rats were supplemented with soybean oil (SO-C, rich in n-6 fatty acids - FA) or hydrogenated vegetable fat (HVF, rich in trans-fatty acids - TFA). Male rats born from the 1st and 2nd generations were maintained in the same supplementation until adulthood, when they were exposed to an amphetamine (AMPH)-induced model of mania and co-treated with Li or not.

KEY FINDINGS

AMPH increased locomotion of both generations and this influence was higher in the HVF than in the SO-C group. Conversely, AMPH increased long-term memory in SO-C group of the 2nd generation. HVF supplementation allowed hippocampal TFA incorporation in rats of both generations (0.1 and 0.2%, respectively). Oxidative parameters indicated higher levels of protein carbonyl (PC) in the HVF group with no changes in catalase (CAT) activity in the 1st generation. In the 2nd generation, AMPH increased PC levels of both experimental groups, whereas CAT activity was lower per se in the HVF group only. The co-treatment with Li leveled out all behavioral parameters, PC levels and CAT activity indicating a significant neuroprotective role.

SIGNIFICANCE

These findings suggest that chronic HVF consumption allows a rising incorporation of TFA in the brain, which may be reflected on the neuropsychiatric conditions related to mania, whereas the effects of Li are not modified in the course of this harmful dietary habit.

http://www.ncbi.nlm.nih.gov/pubmed/25936963

“These findings suggest that chronic hydrogenated vegetable fat consumption **allows a rising incorporation of trans-fatty acids in the brain**, which may be reflected on the **neuropsychiatric conditions related to mania** ...”

“The average Trans Fatty Acid consumption, about 2 g/day, does not seem to affect health. However, an excessive consumption of pastry and confectionery products may present a risk, due not only to Trans Fatty Acid but also to a high consumption of toxic secondary oxidation lipid products. Moreover, because 75% of Trans Fatty Acids in the diet were isomers of industrial origin, their further limitation and monitoring of their level in food seems highly recommendable.”

Journal Of The American College Of Nutrition • July 2015

Consumption Safety of Pastries, Confectioneries, and Potato Products as Related to Fat Content

Author information
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Abstract

STUDY AIM

To determine the content of the main groups of fatty acids in pastries, confectionery, and potato products, paying special attention to trans fatty acids and the products of fat oxidation and hydrolysis, as factors affecting the safety of consumption.

METHODS

A total of 157 products were collected in Poland in 2009-2010. In fats extracted from samples, products of oxidation and hydrolysis were assayed using peroxide (PV), anisidine (AnV), and acid (AV) values. The fatty acid (FA) composition, especially the trans FAs (TFAs) content, was determined by gas chromatography. When assessing the TFA intake, Household Budget Surveys were considered.

RESULTS

Highest content of fat was found for wafers with filling and crisps (32.3% and 29.3%, respectively). In 4 out of 9 groups of pastry and confectionery products studied, the quality of fat was decreased due to an excessive oxidation, as evidenced by a substantial content of secondary products of fat oxidation. The extracted fat was rich in SFA (on average, 50 g SFA/100 g FA) except fries and mixes. A great diversity of TFA content in fat of the products was found (0.1-24.8 g TFA/100 g FA). Wafers were characterized by the highest average content of TFA in the group of pastries (1.94 g TFA/100 g of product). Products of natural origin supplied 0.496 g of TFA per day, and those of industrial origin supplied about 1.5 g.

CONCLUSIONS

The average TFA consumption, about 2 g/day, does not seem to affect health. However, an excessive consumption of pastry and confectionery products may present a risk, due not only to TFA but also to a high consumption of toxic secondary oxidation lipid products. Moreover, because 75% of TFAs in the diet were isomers of industrial origin, their further limitation and monitoring of their level in food seems highly recommendable.

http://www.ncbi.nlm.nih.gov/pubmed/26156640

“Trans fats are associated with all cause mortality, total Coronary Heart Disease, and Coronary Heart Disease mortality.”

BMJ • August 2015

Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies

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Abstract

OBJECTIVE

To systematically review associations between intake of saturated fat and trans unsaturated fat and all cause mortality, cardiovascular disease (CVD) and associated mortality, coronary heart disease (CHD) and associated mortality, ischemic stroke, and type 2 diabetes.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Observational studies reporting associations of saturated fat and/or trans unsaturated fat (total, industrially manufactured, or from ruminant animals) with all cause mortality, CHD/CVD mortality, total CHD, ischemic stroke, or type 2 diabetes.

DATA EXTRACTION AND SYNTHESIS

Two reviewers independently extracted data and assessed study risks of bias. Multivariable relative risks were pooled. Heterogeneity was assessed and quantified. Potential publication bias was assessed and subgroup analyses were undertaken. The GRADE approach was used to evaluate quality of evidence and certainty of conclusions.

RESULTS

For saturated fat, three to 12 prospective cohort studies for each association were pooled (five to 17 comparisons with 90,501-339,090 participants). Saturated fat intake was not associated with all cause mortality (relative risk 0.99, 95% confidence interval 0.91 to 1.09), CVD mortality (0.97, 0.84 to 1.12), total CHD (1.06, 0.95 to 1.17), ischemic stroke (1.02, 0.90 to 1.15), or type 2 diabetes (0.95, 0.88 to 1.03). There was no convincing lack of association between saturated fat and CHD mortality (1.15, 0.97 to 1.36; P=0.10). For trans fats, one to six prospective cohort studies for each association were pooled (two to seven comparisons with 12,942-230,135 participants). Total trans fat intake was associated with all cause mortality (1.34, 1.16 to 1.56), CHD mortality (1.28, 1.09 to 1.50), and total CHD (1.21, 1.10 to 1.33) but not ischemic stroke (1.07, 0.88 to 1.28) or type 2 diabetes (1.10, 0.95 to 1.27). Industrial, but not ruminant, trans fats were associated with CHD mortality (1.18 (1.04 to 1.33) v 1.01 (0.71 to 1.43)) and CHD (1.42 (1.05 to 1.92) v 0.93 (0.73 to 1.18)). Ruminant trans-palmitoleic acid was inversely associated with type 2 diabetes (0.58, 0.46 to 0.74). The certainty of associations between saturated fat and all outcomes was “very low.” The certainty of associations of trans fat with CHD outcomes was “moderate” and “very low” to “low” for other associations.

CONCLUSIONS

Saturated fats are not associated with all cause mortality, CVD, CHD, ischemic stroke, or type 2 diabetes, but the evidence is heterogeneous with methodological limitations. Trans fats are associated with all cause mortality, total CHD, and CHD mortality, probably because of higher levels of intake of industrial trans fats than ruminant trans fats. Dietary guidelines must carefully consider the health effects of recommendations for alternative macronutrients to replace trans fats and saturated fats.

Full text, graphs, charts and 179 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4532752/

Brain Research Bulletin • September 2015

Lifelong consumption of trans fatty acids promotes striatal impairments on Na(+)/K(+) ATPase activity and BDNF mRNA expression in an animal model of mania

Author information

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Abstract

PURPOSE

To evaluate the toxicity of chronic consumption of processed foods that are rich in trans fat on the lipid composition of brain membranes, as well as its functional repercussions.

METHODS

A second generation of male rats born from mothers and grandmothers supplemented with soybean oil (SOC, an isocaloric control group) or hydrogenated vegetable fat (HVF, rich in TFA) (3g/kg; p.o.) were kept under oral treatment until 90 days of age, when they were exposed to an AMPH-induced model of mania.

RESULTS

The HVF group presented 0.38% of TFA incorporation in the striatum, affecting Na(+)/K(+) ATPase activity, which was decreased per se and following AMPH-exposure. The HVF group also showed increased protein carbonyl (PC) and brain-derived neurotrophic factor (BDNF) mRNA levels after AMPH administration, while these oxidative and molecular changes were not observed in the other experimental groups. Additionally, a negative correlation between striatal Na(+)/K(+) ATPase activity and PC levels (r(2)=0.49) was observed.

CONCLUSION

The prolonged consumption of trans fat allows TFA incorporation and increases striatal oxidative status, thus impairing the functionality of Na(+)/K(+)-ATPase and affecting molecular targets as BDNF mRNA. We hypothesized that the chronic intake of processed foods (rich in TFA) facilitates the development of neuropsychiatric diseases, particularly bipolar disorder.

http://www.ncbi.nlm.nih.gov/pubmed/26393778

“the chronic intake of processed foods (rich in Trans Fatty Acids) facilitates the development of neuropsychiatric diseases, **particularly bipolar disorder.**”

“A regulatory policy to eliminate trans fatty acids from processed foods in England would be the most effective and equitable policy option. Intermediate policies would also be beneficial. **Simply continuing to rely on industry to voluntary reformulate products, however, could have negative health and economic outcomes.**”

BMJ • September 2015

Potential of trans fats policies to reduce socioeconomic inequalities in mortality from coronary heart disease in England: cost effectiveness modelling study

Author information
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Abstract

OBJECTIVES
To determine health and equity benefits and cost effectiveness of policies to reduce or eliminate trans fatty acids from processed foods, compared with consumption remaining at most recent levels in England.
DESIGN
Epidemiological modelling study.
SETTING
Data from National Diet and Nutrition Survey, Low Income Diet and Nutrition Survey, Office of National Statistics, and health economic data from other published studies
PARTICIPANTS
Adults aged ≥25, stratified by fifths of socioeconomic circumstance.
INTERVENTIONS
Total ban on trans fatty acids in processed foods; improved labelling of trans fatty acids; bans on trans fatty acids in restaurants and takeaways.
MAIN OUTCOME MEASURES
Deaths from coronary heart disease prevented or postponed; life years gained; quality adjusted life years gained. Policy costs to government and industry; policy savings from reductions in direct healthcare, informal care, and productivity loss.
RESULTS
A total ban on trans fatty acids in processed foods might prevent or postpone about 7200 deaths (2.6%) from coronary heart disease from 2015-20 and reduce inequality in mortality from coronary heart disease by about 3000 deaths (15%). Policies to improve labelling or simply remove trans fatty acids from restaurants/fast food could save between 1800 (0.7%) and 3500 (1.3%) deaths from coronary heart disease and reduce inequalities by 600 (3%) to 1500 (7%) deaths, thus making them at best half as effective. A total ban would have the greatest net cost savings of about £265m (€361m, $415m) excluding reformulation costs, or £64m if substantial reformulation costs are incurred outside the normal cycle.
CONCLUSIONS
A regulatory policy to eliminate trans fatty acids from processed foods in England would be the most effective and equitable policy option. Intermediate policies would also be beneficial. Simply continuing to rely on industry to voluntary reformulate products, however, could have negative health and economic outcomes.

Full text, graphs, charts and 60 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4569940/

“A product intended to extend shelf life has been found to cause myriad health problems.”

American Journal Of Nursing • September 2015

Food Companies Have Three Years to Eliminate Trans Fats

By Carol Potera

Abstract

A product intended to extend shelf life has been found to cause myriad health problems.

http://www.ncbi.nlm.nih.gov/pubmed/26312790

“These data suggest that ruminant trans fatty acids may have beneficial effects on cardiometabolic risk factors conversely to their counterpart industrial trans fatty acids.”

Lipids • September 2015

Natural Rumen-Derived trans Fatty Acids Are Associated with Metabolic Markers of Cardiac Health

Author information

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Abstract

Evidence suggests that industrial trans fatty acids (iTFA) impair lipid profiles while ruminant trans fatty acids (rTFA) may lower insulin resistance and blood pressure. The objective of this article was to determine if the plasma phospholipid percentage of rTFA is associated with a favorable cardiometabolic profile. We collected fasting blood samples from 200 individuals from Quebec city (QC, Canada) aged from 18 to 55 years old, including 100 obese (BMI ≥ 30 kg m(-2)) and 100 non-obese (BMI < 30 kg m(-2)) men and women. Fatty acid levels in plasma phospholipids were determined using gas chromatography. After separating the subjects into two groups, according to the median percentage of rTFA in plasma phospholipids, participants in the group with higher percentages of rTFA (0.86 ± 0.24 %) had higher adiponectin levels ($p = 0.01$) and a lower blood pressure (systolic, $p = 0.005$; diastolic, $p = 0.04$). In contrast, concentrations in plasma phospholipids of elaidic acid, a major iTFA, are positively correlated with glycemia in non-obese subjects ($p = 0.01$) and with both triacylglycerol (TAG) ($p = 0.0007$) and total cholesterol (TC) ($p = 0.009$) in obese subjects. These data suggest that rTFA may have beneficial effects on cardiometabolic risk factors conversely to their counterpart iTFA. Dietary sources of TFA should be taken into account in future cardiometabolic studies.

http://www.ncbi.nlm.nih.gov/pubmed/26210489

“Consumption of hydrogenated vegetable oils and butter were positively associated with an increase risk of metabolic syndrome.”

Diabetes Research And Clinical Practice • November 2015

Is the metabolic syndrome inversely associates with butter, non-hydrogenated- and hydrogenated-vegetable oils consumption: Tehran lipid and glucose study

Abstract

AIM

The aim of this study was to investigate the association between hydrogenated- (HVOs) and non-hydrogenated vegetable oils (non-HVOs) and butter and the metabolic syndrome (MetS) after 3-years of follow-up in adults.

METHODS

This study was conducted between 2006-2008 and 2009-2011 within the framework of the Tehran Lipid and Glucose Study, on 1582 adults, aged 19-84 years. Intakes of HVOs, non-HVOs and butter were assessed by a validated semi-quantitative food frequency questionnaire. Based on the consumption of food rich in fat including HVOs, non-HVOs and butter, participants were categorized to consumers and non-consumers.

RESULTS

Of 1582 participants during a 3-year follow-up, 15.2% developed MetS. Non-consumption of butter was associated with lower MetS risk compared with its consumption. Among consumers of food rich in fat, intake of HVOs and butter were associated with an increased risk of MetS; ORs in the final multivariate model were 2.70 (95% CI: 1.52-4.78) for HVOs and 2.03 (95% CI: 1.20-3.41) for butter, in the highest, compared to the lowest category of dietary intakes. Intake of non-HVOs was not associated with risk of MetS.

CONCLUSIONS

Consumption of HVOs and butter were positively associated with an increase risk of MetS.

http://www.ncbi.nlm.nih.gov/pubmed/26655020

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Journal Of Food Science And Technology • October 2015

Diet containing partially hydrogenated vegetable fat enhances the carrageenan induced paw inflammation but not oxidative stress markers in liver of rats

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Abstract

In the present study, we investigated the effect of feeding Partially hydrogenated vegetable fat (PHVF) on carrageenan induced paw inflammation and oxidative stress markers in liver of rats. In addition, the effect of feeding rats with Linseed Oil (LSO, ß-linolenic acid, n-3 PUFA) or PHVF blended with incremental amounts of LSO on these markers were also monitored. Rats weighing 200 g were given 1 mL of different oils (PHVF, Groundnut Oil; GNO, Olive Oil; OO and LSO) per day for 15 days. Rats given PHVF showed higher levels of paw inflammation in response to carrageenan injection. Rats given LSO showed least amounts of paw inflammation when injected with carrageenan. A second set of experiment was conducted by feeding weaning rats with AIN-93 purified diet supplemented with PHVF or PHVF with incremental amounts of LSO for 60 days. The rats fed PHVF showed higher degree of carrageenan induced inflammation as compared to rats given GNO and LSO. However, the rats fed PHVF showed lower levels of lipid peroxides, protein carbonyls, 8-hydroxy guanine and antioxidant enzyme activities in liver homogenate as compared to those given LSO. In conclusion dietary PHVF rendered the rats prone to higher levels of carrageenan induced inflammation which can be reduced by giving PHVF blended with LSO. However, oxidative stress markers found to be higher levels in rats given LSO or PHVF blended with LSO as compared to rats given PHVF as sole source of fat.

http://www.ncbi.nlm.nih.gov/pubmed/26396384

“In conclusion dietary Partially hydrogenated vegetable fat rendered the rats prone to higher levels of **carrageenan induced inflammation**...”

“Obesity and overweight are major public health problems. Various factors, such as daily nutritional habits, physical inactivity, and genetic, are related to the prevalence of obesity. **Recently, it was revealed that the gut microflora may also play an important role in weight management.**”

Food Nutrition Research • December 2015

The anti-obesity effects of Lactobacillus casei strain Shirota versus Orlistat on high fat diet-induced obese rats

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Abstract

BACKGROUND

Obesity and overweight are major public health problems. Various factors, such as daily nutritional habits, physical inactivity, and genetic, are related to the prevalence of obesity. Recently, it was revealed that the gut microflora may also play an important role in weight management. Thus, this study aimed to determine the anti-obesity effects of Lactobacillus casei strain Shirota (LcS) compared with those of orlistat in an animal model fed a high-fat diet (HFD).

DESIGN

Thirty-two male Sprague-Dawley rats were assigned to four groups fed various diets as follows: a standard diet group, HFD group, HFD supplemented with LcS (108109 colony-forming units (HFD-LcS) group, and HFD group treated with Orlistat (10 mg/kg body weight)). After 15 weeks, the weights of organs, body weight, body fat mass and serological biomarkers were measured. In addition, histological analysis of the liver and adipose tissue was performed.

RESULTS

Body weight, body mass index, fat mass, leptin and glucose levels were lower, and high-density lipoprotein and adiponectin levels were higher in the HFD-LcS and HFD-orlistat groups than in the HFD group. In addition a significant difference in body fat mass was observed between HFD-LcS group with HFD-orlistat group (19.19±5.76 g vs. 30.19±7.98 g). Although the interleukin-6 level was significantly decreased in the HFD-LcS and HFD-orlistat groups compared with the HFD group, no significant change was observed in other inflammatory biomarkers.

CONCLUSION

The results of the present study show that LcS supplementation improves body weight management and the levels of some related biomarkers. In addition, LcS supplementation showed a better result in fat mass and alanine aminotransferase reduction than Orlistat. Further studies are needed to elucidate the anti-obesity effects of LcS, with a longer period of supplementation.

Full text, graphs, charts and 51 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856475/

“Adverse effects of industrially produced trans fatty acids on the risk of coronary artery disease are well documented in the scientific literature.”

American Journal Of Clinical Nutrition • December 2015

Vaccenic acid and trans fatty acid isomers from partially hydrogenated oil both adversely affect LDL cholesterol: a double-blind, randomized controlled trial

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Abstract

BACKGROUND

Adverse effects of industrially produced trans fatty acids (iTFAs) on the risk of coronary artery disease are well documented in the scientific literature; however, effects of naturally occurring trans fatty acids (TFAs) from ruminant animals (rTFA), such as vaccenic acid (VA) and cis-9,trans-11 conjugated linoleic acid (c9,t11-CLA), are less clear. Although animal and cell studies suggest that VA and c9,t11-CLA may be hypocholesterolemic and antiatherogenic, epidemiologic data comparing rTFAs and iTFAs are inconsistent, and human intervention studies have been limited, underpowered, and not well controlled.

OBJECTIVE

We determined the effects of VA, c9,t11-CLA, and iTFA, in the context of highly controlled diets (24 d each), on lipoprotein risk factors compared with a control diet.

RESULTS

We conducted a double-blind, randomized, crossover feeding trial in 106 healthy adults [mean ± SD age: 47 ± 10.8 y; body mass index (in kg/m(2)): 28.5 ± 4.0; low-density lipoprotein (LDL) cholesterol: 3.24 ± 0.63 mmol/L]. Diets were designed to have stearic acid replaced with the following TFA isomers (percentage of energy): 0.1% mixed isomers of TFA (control), ~3% VA, ~3% iTFA, or 1% c9,t11-CLA. Total dietary fat (34% of energy) and other macronutrients were matched. Total cholesterol (TC), LDL cholesterol, triacylglycerol, lipoprotein(a), and apolipoprotein B were higher after VA than after iTFA; high-density lipoprotein (HDL) cholesterol and apolipoprotein AI also were higher after VA. Compared with control, VA and iTFA both increased TC, LDL cholesterol, ratio of TC to HDL cholesterol, and apolipoprotein B (2-6% change; $P < 0.05$); VA also increased HDL cholesterol, apolipoprotein AI, apolipoprotein B, and lipoprotein(a) (2-6% change; $P < 0.05$), whereas iTFA did not. c9,t11-CLA lowered triacylglycerol ($P \leq 0.01$) and had no effect on other lipoprotein risk factors.

CONCLUSIONS

With respect to risk of cardiovascular disease, these results are consistent with current nutrition labeling guidelines, with the requirement of VA, but not c9,t11-CLA, to be listed under TFA on the Nutrition Facts Panel. This trial was registered at clinicaltrials.gov as NCT00942656.

http://www.ncbi.nlm.nih.gov/pubmed/26561632

“Intakes of monounsaturated fatty acids and polyunsaturated fatty acids were associated with a lower risk of cardiovascular disease and death, whereas saturated fatty acid and trans-fat intakes were associated with a higher risk of cardiovascular disease.”

American Journal Of Clinical Nutrition • December 2015

Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease

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Abstract

BACKGROUND

Dietary fat quality and fat replacement are more important for cardiovascular disease (CVD) prevention than is total dietary fat intake.

OBJECTIVE

The aim was to evaluate the association between total fat intake and fat subtypes with the risk of CVD (myocardial infarction, stroke, or death from cardiovascular causes) and cardiovascular and all-cause death. We also examined the hypothetical effect of the isocaloric substitution of one macronutrient for another.

DESIGN

We prospectively studied 7038 participants at high CVD risk from the PREvención con DIeta MEDiterránea (PREDIMED) study. The trial was conducted from 2003 to 2010, but the present analysis was based on an expanded follow-up until 2012. At baseline and yearly thereafter, total and specific fat subtypes were repeatedly measured by using validated food-frequency questionnaires. Time-dependent Cox proportional hazards models were used.

RESULTS

After 6 y of follow-up, we documented 336 CVD cases and 414 total deaths. HRs (95% CIs) for CVD for those in the highest quintile of total fat, monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA) intake compared with those in the lowest quintile were 0.58 (0.39, 0.86), 0.50 (0.31, 0.81), and 0.68 (0.48, 0.96), respectively. In the comparison between extreme quintiles, higher saturated fatty acid (SFA) and trans-fat intakes were associated with 81% (HR: 1.81; 95% CI: 1.05, 3.13) and 67% (HR: 1.67; 95% CI: 1.09, 2.57) higher risk of CVD. Inverse associations with all-cause death were also observed for PUFA and MUFA intakes. Isocaloric replacements of SFAs with MUFAs and PUFAs or trans fat with MUFAs were associated with a lower risk of CVD. SFAs from pastries and processed foods were associated with a higher risk of CVD.

CONCLUSIONS

Intakes of MUFAs and PUFAs were associated with a lower risk of CVD and death, whereas SFA and trans-fat intakes were associated with a higher risk of CVD. The replacement of SFAs with MUFAs and PUFAs or of trans fat with MUFAs was inversely associated with CVD. This trial was registered at www.controlled-trials.com as ISRCTN 35739639.

http://www.ncbi.nlm.nih.gov/pubmed/26561617

“As assessed through surveys and inspections, **the trans fat ban** in Nassau County yielded relatively high compliance rates within 2 years and was accepted by sanitarians, establishment operators, and consumers.”

Clinical Therapeutics • March 2014

First time compliance inspections to evaluate an artificial trans fat ban in Nassau County

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Abstract

BACKGROUND

In 2007, Nassau County, New York, restricted the use of artificial trans fats in food establishments licensed by the Nassau County Department of Health (NCDH). The regulation took effect April 1, 2008.

OBJECTIVE

This study assesses first-time inspection compliance rates with the trans fat ban and examines barriers to enforcement.

RESULTS

A total of 360 food service establishments were randomly selected for inspection; 328 completed the operator surveys. Compliance was 81%, even though 52% of operators were not aware of the ban. Of those who were aware, 57% heard about the regulation from the media, and almost all (92%) reported that compliance with the ban was easy. Of noncompliant respondents, 59% cited lack of knowledge regarding the ban as the primary reason for noncompliance. Of those who indicated they had received any customer feedback (9%), almost all reported the feedback to be positive. Knowledge of trans fats was not associated with compliance, but owners who were aware of the ban were more likely to be in compliance. Among the 23 participating sanitarians, 96% believed the ban was effective; language barriers were cited as the primary obstacle to enforcement.

CONCLUSIONS

As assessed through surveys and inspections, the trans fat ban in Nassau County yielded relatively high compliance rates within 2 years and was accepted by sanitarians, establishment operators, and consumers.

http://www.ncbi.nlm.nih.gov/pubmed/24636819

“Two key challenges to the health industry arise from this evidence. They must first determine whether a small intake of Trans Fatty Acids from partially hydrogenated vegetable oil is safe and what constitutes a safe amount. They must also determine whether Trans Fatty Acids from ruminant fat in currently consumed amounts represent limited cardiovascular risk that is balanced by the nutritional benefits of dairy products.”

Clinical Therapies • March 2014

Trans fatty acids: are its cardiovascular risks fully appreciated?

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Abstract

OBJECTIVE

The goal of this article was to review the causal link between trans fatty acids (TFA) produced from partially hydrogenated vegetable oil (PHVO) and cardiovascular disease (CVD) risk and its likely mechanisms. The potential risk of TFA from ruminant dairy and meats, which are currently the major sources of dietary TFA, is also discussed.

METHODS

Evidence was derived from observational studies of large cohorts followed up prospectively; from randomized controlled trials of clinical interventions; and from specific case-control studies that investigated biomarkers in tissues. Searches included PubMed and Medline from 1990 to 2013.

RESULTS

Despite TFA from PHVO being associated more strongly with CVD risk than even saturated fats, it may prove difficult to totally eliminate PHVO from all foods. This raises the issue of the lower limit of TFA consumption below which CVD risk is not increased. Limits of <1% of total energy have been suggested. The major mechanism underlying the increased CVD risk from TFA is an increase in LDL-C and Lp(a) lipoproteins and a decrease in HDL-C; increased inflammation and adverse effects on vascular function have also been shown. Both PHVO and ruminant TFA comprise a range of isomers, some specific to each source but including a substantial commonality that supports findings of similar adverse effects at equivalent intakes of TFA. However, the amount of TFA in ruminant fat is relatively small; this limits the CVD risk from eating ruminant products, an inference supported by analysis of prospective cohort studies.

CONCLUSIONS

Two key challenges to the health industry arise from this evidence. They must first determine whether a small intake of TFA from PHVO is safe and what constitutes a safe amount. They must also determine whether TFA from ruminant fat in currently consumed amounts represent limited cardiovascular risk that is balanced by the nutritional benefits of dairy products.

http://www.ncbi.nlm.nih.gov/pubmed/24636816

“... nut and olive oil intake is associated with reduced Cardiovascular Disease risk. In conclusion, the total matrix of a food is more important than just its fatty acid content in predicting the effect of a food on Cardiovascular Disease risk, and a healthy diet should be the cornerstone of Cardiovascular Disease prevention.”

Atherosclerosis • June 2014

Dietary fats and cardiovascular disease: putting together the pieces of a complicated puzzle

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Abstract

Dietary fatty acids play significant roles in the cause and prevention of cardiovascular disease (CVD). Trans fatty acids from partially hydrogenated vegetable oils have well-established adverse effects and should be eliminated from the human diet. CVD risk can be modestly reduced by decreasing saturated fatty acids (SFA) and replacing it by a combination of polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA). Although the ideal type of unsaturated fat for this replacement is unclear, the benefits of PUFA appear strongest. Both n-6 and n-3 PUFA are essential and reduce CVD risk. However, additional research is needed to better define the optimal amounts of both and to discern the patients and/or general population that would benefit from supplemental n-3 fatty acid intake. Furthermore, consumption of animal products, per se, is not necessarily associated with increased CVD risk, whereas nut and olive oil intake is associated with reduced CVD risk. In conclusion, the total matrix of a food is more important than just its fatty acid content in predicting the effect of a food on CVD risk, and a healthy diet should be the cornerstone of CVD prevention.

http://www.ncbi.nlm.nih.gov/pubmed/24727233

“...trans fat may be harmful to skin health by making it more vulnerable to Ultra Violet Ray injury and thus **more prone to develop photoaging and skin cancer.**”

Food And Chemical Toxicology • July 2014

Cross-generational trans fat intake exacerbates UV radiation-induced damage in rat skin

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Abstract

We evaluated the influence of dietary fats on ultraviolet radiation (UVR)-induced oxidative damage in skin of rats. Animals from two consecutive generations born of dams supplemented with fats during pregnancy and breastfeeding were maintained in the same supplementation: soybean-oil (SO, rich in n-6 FA, control group), fish-oil (FO, rich in n-3 FA) or hydrogenated-vegetable-fat (HVF, rich in TFA). At 90 days of age, half the animals from the 2nd generation were exposed to UVR (0.25 J/cm(2)) 3×/week for 12 weeks. The FO group presented higher incorporation of n-3 FA in dorsal skin, while the HVF group incorporated TFA. Biochemical changes per se were observed in skin of the HVF group: greater generation of reactive oxygen species (ROS), lower mitochondrial integrity and increased Na(+)K(+)-ATPase activity. UVR exposure increased skin wrinkles scores and ROS generation and decreased mitochondrial integrity and reduced-glutathione levels in the HVF group. In FO, UVR exposure was associated with smaller skin thickness and reduced levels of protein-carbonyl, together with increased catalase activity and preserved Na(+)K(+)-ATPase function. In conclusion, while FO may be protective, trans fat may be harmful to skin health by making it more vulnerable to UVR injury and thus more prone to develop photoaging and skin cancer.

Full text, downloadable PDF with Graphs, Charts and 90 references

http://www.sciencedirect.com/science/article/pii/S0278691514001604

Preventing Chronic Disease • August 2014

Prevalence of partially hydrogenated oils in US packaged foods, 2012

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Abstract

“Although there is evidence that consumption of trans fat has declined in the United States, limited documentation exists on current levels of industrial trans fat in foods. We estimated the prevalence of partially hydrogenated oils in 4,340 top-selling US packaged foods. **Nine percent of products in the sample contained partially hydrogenated oils; 84% of these products listed “0 grams” of trans fat per serving, potentially leading consumers to underestimate their trans fat consumption.** Government efforts to eliminate partially hydrogenated oils from packaged foods will substantially reduce exposure to this known cardiovascular disease risk factor.”

Full text with 7 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4149331/

The Journal Of The American Heart Association • August 2014

Plasma phospholipid trans-fatty acids levels, cardiovascular diseases, and total mortality: the cardiovascular health study

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Abstract

BACKGROUND

While self-reported trans-fatty acid (TFA) consumption is linked to coronary heart disease (CHD), relationships between objective biomarkers of TFA subtypes (t-16:1n9, total t-18:1, and cis/trans-(c/t-), t/c- and t/t-18:2) and cardiovascular disease (CVD) or total mortality are not well established.

METHODS AND RESULTS

We evaluated 2742 adults in the Cardiovascular Health Study, aged 74±5 years and free of prevalent CVD, with plasma phospholipid TFA measures in 1992. Incident fatal and nonfatal CHD events, CVD and non-CVD mortality, and total mortality were centrally adjudicated through 2010. Risks were assessed using Cox proportional hazards. During 31 494 person-years, 1735 total deaths and 639 total CHD events occurred. In the multivariate model including mutual adjustment for the 5 TFA subtypes, circulating t/t-18:2 was associated with higher total mortality (extreme quintile hazard ratio (HR)=1.23, 95% CI=1.04 to 1.44, P-trend=0.01), CVD mortality (HR=1.40, 95% CI=1.05 to 1.86, P-trend=0.02), and total CHD (HR=1.39, 95% CI=1.06 to 1.83, P-trend=0.01). t/c-18:2 was positively related to total mortality (HR=1.19, P-trend=0.05), total CHD (HR=1.67, P-trend=0.002), and nonfatal CHD (HR=2.06, P-trend=0.002) after mutual adjustment; these associations were insignificant without mutual adjustment. Neither t-16:1n9 nor t-18:1 was significantly associated with total mortality or CVD, nor was c/t-18:2 if we excluded early cases.

CONCLUSIONS

Among circulating TFAs, t/t-18:2 was most adversely associated with total mortality, mainly due to the increased risk of CVD. t/c-18:2 was also positively associated with total mortality and CHD, but only after adjustment for other TFAs. These results highlight the need for further investigation of dietary sources, nondietary determinants, and health effects of specific TFA subtypes, especially t-18:2 isomers.

Full text, graphs, charts and 64 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4310377/

“... chronic trans fatty acids consumption from weaning is able to **favor the development of neuromotor and neuropsychiatric diseases**, whose intensity was time dependent.”

International Journal Of Food Science And Nutrition • September 2014

Prolonged consumption of trans fat favors the development of orofacial dyskinesia and anxiety-like symptoms in older rats

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Abstract

Polyunsaturated fatty acids (FAs) are cell membrane components involved in brain functions. We hypothesized that long-term trans fat consumption is able to modify the membrane FAs composition impairing behavioral parameters related to aging. In this study, a comparison of behavioral parameters at 10 and 15 months of trans fat consumption by male Wistar rats was made. Animals were fed for 10 and 15 months from weaning with diets containing either 20% w/w soybean oil (SO), rich in n-6 PUFA, hydrogenated vegetable fat (HVF), rich in trans FAs, or a standard diet (control - C). At both evaluation times, HVF-fed rats showed progressively increased parameters of orofacial dyskinesia, fear and anxiety-like symptoms. The HVF diet reduced locomotor and exploratory activities progressively over 10 and 15 months of supplementation, while the standard and SO diets did not. In this study, we showed that chronic trans FAs consumption from weaning is able to favor the development of neuromotor and neuropsychiatric diseases, whose intensity was time dependent.

http://www.ncbi.nlm.nih.gov/pubmed/24625052

“Chronic consumption of processed food causes structural changes in membrane phospholipids, affecting brain neurotransmission. As brain incorporation of trans and n-6 PUFA [Omega 6 Polyunsaturated Fatty Acids] modifies its physiological functions, **it may facilitate drug addiction.”**

Toxicology Letters • October 2014

Toxicological aspects of trans fat consumption over two sequential generations of rats: Oxidative damage and preference for amphetamine

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Abstract

Chronic consumption of processed food causes structural changes in membrane phospholipids, affecting brain neurotransmission. Here we evaluated noxious influences of dietary fats over two generations of rats on amphetamine (AMPH)-conditioned place preference (CPP). Female rats received soybean oil (SO, rich in n-6 fatty acids (FA)), fish oil (FO, rich in n-3 FA) and hydrogenated vegetable fat (HVF, rich in trans fatty acids (TFA)) for two successive generations. Male pups from the 2nd generation were maintained on the same supplementation until 41 days of age, when they were conditioned with AMPH in CPP. While the FO group showed higher incorporation of n-3 polyunsaturated-FA (PUFA) in cortex/hippocampus, the HVF group showed TFA incorporation in these same brain areas. The SO and HVF groups showed AMPH-preference and anxiety-like symptoms during abstinence. Higher levels of protein carbonyl (PC) and lower levels of non-protein thiols (NPSH) were observed in cortex/hippocampus of the HVF group, indicating antioxidant defense system impairment. In contrast, the FO group showed no drug-preference and lower PC levels in cortex. Cortical PC was positively correlated with n-6/n-3 PUFA ratio, locomotion and anxiety-like behavior, and hippocampal PC was positively correlated with AMPH-preference, reinforcing connections between oxidative damage and AMPH-induced preference/abstinence behaviors. As brain incorporation of trans and n-6 PUFA modifies its physiological functions, it may facilitate drug addiction.

http://www.ncbi.nlm.nih.gov/pubmed/25290576

“In conclusion, diets high in trans Fatty acids, processed meats, and higher fat dairy products were positively associated with non-Hodgkin lymphoma risk, whereas diets high in n3 fatty acids and total seafood were inversely associated with risk.”

Journal Of Nutrition • May 2013

Trans fatty acid intake is associated with increased risk and n3 fatty acid intake with reduced risk of non-hodgkin lymphoma

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Abstract

We evaluated the association of dietary fat and protein intake with risk of non-Hodgkin lymphoma (NHL) in a clinic-based study in 603 cases (including 218 chronic lymphocytic leukemia/small lymphocytic lymphoma, 146 follicular lymphoma, and 105 diffuse large B-cell lymphoma) and 1007 frequency-matched controls. Usual diet was assessed with a 128-item food-frequency questionnaire. Unconditional logistic regression was used to estimate ORs and 95% CIs, and polytomous logistic regression was used to assess subtype-specific risks. trans Fatty acid (TFA) intake was positively associated with NHL risk [OR = 1.60 for highest vs. lowest quartile (95% CI = 1.18, 2.15); P-trend = 0.0014], n3 (ß3) fatty acid intake was inversely associated with risk [OR = 0.48 (95% CI = 0.35, 0.65); P-trend < 0.0001], and there was no association with total, animal, plant-based, or saturated fat intake. When examining intake of specific foods, processed meat [OR = 1.37 (95% CI = 1.02, 1.83); P-trend = 0.03], milk containing any fat [OR = 1.47 (95% CI = 1.16, 1.88); P-trend = 0.0025], and high-fat ice cream [OR = 4.03 (95% CI = 2.80, 5.80); P-trend < 0.0001], intakes were positively associated with risk, whereas intakes of fresh fish and total seafood [OR = 0.61 (95% CI = 0.46, 0.80); P-trend = 0.0025] were inversely associated with risk. Overall, there was little evidence for NHL subtype-specific heterogeneity. In conclusion, diets high in TFAs, processed meats, and higher fat dairy products were positively associated with NHL risk, whereas diets high in n3 fatty acids and total seafood were inversely associated with risk.

Full text, graphs, charts and 43 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3738236/

“A substantial inclusion of **processed foods**, instead of foods rich in omega-3, in the long term **is able to influence the functionality of brain structures related to behavioral disturbances and weaker neuroprotection,** whose impact should be considered by food safety authorities and psychiatry experts.”

Progress In Neuropsychopharmacology & Biological Psychiatry • August 2013

Influence of lifelong dietary fats on the brain fatty acids and amphetamine-induced behavioral responses in adult rat

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Abstract

The influence of dietary fatty acids (FA) on mania-like behavior and brain oxidative damage were evaluated in rats. First generation of rats born and maintained under supplementation with soybean-oil (SO), fish-oil (FO) or hydrogenated-vegetable-fat (HVF), which are rich in n-6, n-3 and trans (TFA) FA, respectively, until adulthood, were exposed to an amphetamine (AMPH)-induced mania animal model to behavioral and biochemical evaluations. While AMPH caused hyperlocomotion in HVF and, to a less extent, in SO- and FO-groups, a better memory performance was observed in FO group. Among vehicle-groups, HVF increased reactive species (RS) generation and protein-carbonyl (PC) levels in cortex; FO reduced RS generation in hippocampus and decreased PC levels in hippocampus and striatum. Among AMPH-treated animals, HVF exacerbated RS generation in all evaluated brain areas and increased PC levels in cortex and striatum; FO reduced RS generation in hippocampus and decreased PC levels in hippocampus and striatum. FO was related to higher percentage of polyunsaturated fatty acids (PUFA) and docosahexaenoic acid (DHA) in cortex and striatum, while HVF was associated to higher incorporation of TFA in cortex, hippocampus and striatum, besides increased n-6/n-3 FA ratio in striatum. While a continuous exposure to TFA may intensify oxidative events in brain, a prolonged FO consumption may prevent mania-like-behavior; enhance memory besides decreasing brain oxidative markers. A substantial inclusion of processed foods, instead of foods rich in omega-3, in the long term is able to influence the functionality of brain structures related to behavioral disturbances and weaker neuroprotection, whose impact should be considered by food safety authorities and psychiatry experts.

http://www.ncbi.nlm.nih.gov/pubmed/23791617

“Our results showed the beneficial effects of Fish Oil supplementation, as well as **the harmful effects of trans Fatty Acids**, whose intensity **can increase vulnerability to skin diseases.**”

Lipids • October 2013

Trans fat supplementation increases UV-radiation-induced oxidative damage on skin of mice

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Abstract

We evaluated the influence of fish oil (FO, rich in n-3 FA), soybean oil (SO, rich in n-6 FA) and hydrogenated vegetable fat (HVF, rich in trans FA) on the oxidative status and viability of skin cells of mice exposed to ultraviolet radiation (UVR). Mice were supplemented with FO, SO or HVF for three months and exposed to UVR (2.72 mJ/cm(2)) for 2 days. One day after the last UVR session, the FO group showed higher levels of n-3 fatty acids (FA), while the HVF showed higher incorporation of trans FA (TFA) in dorsal skin. UVR increased lipid peroxidation and protein carbonyl levels of the HVF and to a lesser extent of the control and SO groups. Although all irradiated groups showed increased skin thickness, this increase was slighter in FO mice. UVR exposure reduced skin cell viability of the control, SO and HVF groups, while FO prevented this. Catalase activity was reduced independently of the supplementation and SOD level was increased in C and FO groups after UVR exposure; FO prevented the UVR-induced increase in glutathione levels, which was observed in skin of the control, SO and HVF mice. Our results showed the beneficial effects of FO supplementation, as well as the harmful effects of trans FA, whose intensity can increase vulnerability to skin diseases.

http://www.ncbi.nlm.nih.gov/pubmed/23737082

“This review describes **pro-inflammatory effects of Trans Fatty Acids** in our diet on various **systemic disorders** and also discusses a possible role of Trans Fatty Acids on **gut inflammation.**”

Journal Of Gastroenterology & Hepatology • December 2013

Trans fatty acids in diets act as a precipitating factor for gut inflammation?

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Abstract

Fatty acids in our daily diet are broadly classified into cis and trans fatty acids (TFAs). TFAs are formed during the manufacturing process of hydrogenated vegetable oils such as margarine. Modern diets such as deep-fried products, frozen foods, and packaged snacks commonly include large quantities of margarine containing TFAs. Although an increased report in the effects of the diet containing TFAs on a risk factor of metabolic syndrome, diabetes mellitus, and coronary heart disease has been observed in the recent years, influence on intestinal inflammation remains unknown. This review describes pro-inflammatory effects of TFAs in our diary diet on various systemic disorders and also discusses a possible role of TFAs on gut inflammation.

http://www.ncbi.nlm.nih.gov/pubmed/24251700

“Trans fatty acids suppress prostacyclin production at levels found in commercial margarines, and processed foods labeled as trans-free could contribute to this effect if consumed in multiple servings or in addition to foods containing larger amounts of trans fats.”

Scandinavian Cardiovascular Journal • December 2013

Effects of trans fats on prostacyclin production

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Abstract

OBJECTIVES

Prostacyclin is a prostanoid derived from arachidonic acid that prevents thrombosis and is thereby expected to protect against heart disease, while trans fats present in partially hydrogenated oils interfere with arachidonic acid metabolism. Therefore, the objective of the present study was to investigate how fats with different proportions of linoleic acid and trans-18:1 affect prostacyclin released by cultured endothelial cells, and to compare these proportions with those found in commercially available foods.

DESIGN

Soybean oil and hydrogenated soybean oil (coating fat) were mixed in different proportions to yield seven fat mixtures with proportions of linoleic acid ranging from 54.1% to 5.7% and trans-18:1 acid ranging from 0.4% to 43.9%. Human endothelial cells were cultured in each of the mixtures, and their phospholipid fractions were then separated and their fatty acids were analyzed by gas chromatography. The prostacyclin released by the cells was measured using RIA kits. Margarines and processed foods were purchased from the supermarket for comparison.

RESULTS

Our work revealed that as the percentage of trans fat was increased, the amount of prostacyclin released dose-dependently and significantly ($P < 0.0001$) decreased, the concentration of linoleic and arachidonic acid decreased in the membrane phospholipids while the concentration of trans 18:1 acids increased, the prostacyclin decreased by 35-98%. Supermarket margarines had levels of trans fats similar to those that suppressed prostacyclin by 35-54%. Most processed foods labeled as trans-free contained trans fats.

CONCLUSIONS

Trans fatty acids suppress prostacyclin production at levels found in commercial margarines, and processed foods labeled as trans-free could contribute to this effect if consumed in multiple servings or in addition to foods containing larger amounts of trans fats.

http://www.ncbi.nlm.nih.gov/pubmed/24228623

Pharmacology And Biochemical Behavior • January 2011

Comparative study between n-6, trans and n-3 fatty acids on repeated amphetamine exposure: a possible factor for the development of mania

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Abstract

In the last decades, foods rich in omega-3 (Omega-3) fatty acids (FA) have been replaced by omega-6 (Omega-6) and trans FA, which are found in processed foods. The influence of Omega-6 (soybean oil--SO), trans (hydrogenated vegetable fat--HVF) and Omega-3 (fish oil--FO) fatty acids on locomotor and oxidative stress (OS) parameters were studied in an animal model of mania. Rats orally fed with SO, HVF and FO for 8 weeks received daily injections of amphetamine (AMPH--4 mg/kg/mL-ip) for the last week of oral supplementation. HVF induced hyperactivity, increased the protein carbonyl levels in the cortex and decreased the mitochondrial viability in cortex and striatum. AMPH-treatment increased the locomotion and decreased the mitochondrial viability in all groups, but its neurotoxicity was higher in the HVF group. Similarly, AMPH administration increased the protein carbonyl levels in striatum and cortex of HVF-supplemented rats. AMPH reduced the vitamin-C plasmatic levels of SO and HVF-fed rats, whereas no change was observed in the FO group. Our findings suggest that trans fatty acids increased the oxidative damage per se and exacerbated the AMPH-induced effects. The impact of trans fatty acids consumption on neuronal diseases and its consequences in brain functions must be further evaluated.

http://www.ncbi.nlm.nih.gov/pubmed/21078338

“Our findings suggest that trans fatty acids **increased the oxidative damage** per se and exacerbated the AMPH-induced [amphetamine-induced] effects. The impact of trans fatty acids consumption on neuronal diseases and its consequences in brain functions must be further evaluated.”

“... high consumption of Hydrogenated Vegetable Oils was associated with a greater risk of having **dyslipidaemia, hypertension** [or] at least one [or] two risk factors [for hypertension]...”

British Journal Of Nutrition • March 2011

Different kinds of vegetable oils in relation to individual cardiovascular risk factors among Iranian women

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Abstract

Detrimental effects of trans-fats on lipid profiles, blood pressure and plasma glucose levels have been documented by short-term clinical trials with high doses of trans-fats, but limited observational studies have considered habitual consumption of partially hydrogenated vegetable oil (PHVO) and these outcome variables, particularly hypertension. We aimed to evaluate the association of PHVO and non-hydrogenated vegetable oils (non-HVO) intake with individual cardiovascular risk factors. In a cross-sectional study of 486 Iranian adult women, usual dietary intakes were assessed, and fasting plasma glucose (FPG), lipid profiles and blood pressure were measured. PHVO (commonly used for cooking in Iran) were considered as the PHVO category. Sunflower oil, maize oil, rapeseed oil, soyabean oil and olive oil were defined as the non-HVO category. Diabetes (FPG ≥ 1260 mg/l), dyslipidaemia (based on Adult Treatment Panel III) and hypertension (based on Joint National Committee VI) were defined. The presence of ‘at least one risk factor’ and ‘at least two risk factors’ of the three major risk factors for CVD (hypertension, dyslipidaemia and diabetes) was also evaluated. After controlling for age and other potential confounders, a high consumption of HVO was associated with a greater risk of having dyslipidaemia (OR for top v. bottom quintile 5·04; 95 % CI 2·70, 9·36), hypertension (OR for top v. bottom quintile 3·03; 95 % CI 1·55, 6·10), at least one (OR for top v. bottom quintile 8·52; 95 % CI 4·41, 16·41) and at least two risk factors (OR for top v. bottom quintile 3·60; 95 % CI 1·64, 7·74), while those in the top quintile of non-HVO consumption had lower odds for all these conditions. Further adjustment for dietary intakes had little impact on these associations. Even after additional adjustment for BMI, the positive association of HVO and the inverse association of non-HVO with the above-mentioned cardiovascular risk factors remained significant, except for the association between non-HVO and hypertension that became marginally significant. No overall significant associations were found between the consumption of HVO and non-HVO and diabetes. Higher intakes of PHVO were associated with a greater risk of individual cardiovascular risk factors, while those of non-HVO were associated with a reduced risk.

http://www.ncbi.nlm.nih.gov/pubmed/21251338

“It seems that a strong relationship exists between the consumption of Trans Fatty Acids in the oxidized oils and lipid peroxidation and **non alcoholic fatty liver disease (NAFLD).**”

Nutritional Metabolism London • September 2011

The intake of high fat diet with different trans fatty acid levels differentially induces oxidative stress and non alcoholic fatty liver disease (NAFLD) in rats

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Abstract

BACKGROUND

Trans-fatty acids (TFA) are known as a risk factor for coronary artery diseases, insulin resistance and obesity accompanied by systemic inflammation, the features of metabolic syndrome. Little is known about the effects on the liver induced by lipids and also few studies are focused on the effect of foods rich in TFAs on hepatic functions and oxidative stress. This study investigates whether high-fat diets with different TFA levels induce oxidative stress and liver dysfunction in rats.

METHODS

Male Wistar rats were divided randomly into four groups (n = 12/group): C receiving standard-chow; Experimental groups that were fed high-fat diet included 20% fresh soybean oil diet (FSO), 20% oxidized soybean oil diet (OSO) and 20% margarine diet (MG). Each group was kept on the treatment for 4 weeks.

RESULTS

A liver damage was observed in rats fed with high-fat diet via increase of liver lipid peroxidation and decreased hepatic antioxidant enzyme activities (superoxide dismutase, catalase and glutathione peroxidase). The intake of oxidized oil led to higher levels of lipid peroxidation and a lower concentration of plasma antioxidants in comparison to rats fed with FSO. The higher inflammatory response in the liver was induced by MG diet. Liver histopathology from OSO and MG groups showed respectively moderate to severe cytoplasm vacuolation, hypatocyte hypertrophy, hepatocyte ballooning, and necroinflammation.

CONCLUSION

It seems that a strong relationship exists between the consumption of TFA in the oxidized oils and lipid peroxidation and non alcoholic fatty liver disease (NAFLD). The extent of the peroxidative events in liver was also different depending on the fat source suggesting that feeding margarine with higher TFA levels may represent a direct source of oxidative stress for the organism. The present study provides evidence for a direct effect of TFA on NAFLD.

Full text, Graphs, Charts and 66 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3192664/

“increasing epidemiologic and biochemical evidence suggest that excessive trans fats in the diet are a significant risk factor for cardiovascular events. **A 2% absolute increase in energy intake from trans fat has been associated with a 23% increase in cardiovascular risk.**”

Journal Of The American Dietetic Association • April 2010

Trans fats in America: a review of their use, consumption, health implications, and regulation

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Abstract

Trans fatty acids have long been used in food manufacturing due in part to their melting point at room temperature between saturated and unsaturated fats. However, increasing epidemiologic and biochemical evidence suggest that excessive trans fats in the diet are a significant risk factor for cardiovascular events. A 2% absolute increase in energy intake from trans fat has been associated with a 23% increase in cardiovascular risk. Although Denmark has shown it is possible to all but eliminate commercial sources of trans fats from the diet, total elimination is not possible in a balanced diet due to their natural presence in dairy and meat products. Thus, the American Heart Association recommends limiting trans fats to <1% energy, and the American Dietetic Association, the Institute of Medicine, US Dietary Guidelines, and the National Cholesterol Education Project all recommend limiting dietary trans-fat intake from industrial sources as much as possible. The presence of small amounts of trans fat in hydrogenated or partially hydrogenated oils/food products will likely cause many Americans to exceed their recommended maximum. This likelihood is exacerbated by the Food and Drug Administration labeling rules, which allow products containing <0.5 g trans fat per serving to claim 0 g trans fat. Many products with almost 0.5 g trans fat, if consumed over the course of a day, may approximate or exceed the 2 g maximum as recommended by American Heart Association, all while claiming to be trans-fat free. Accordingly, greater transparency in labeling and/or active consumer education is needed to reduce the cardiovascular risks associated with trans fats.

http://www.ncbi.nlm.nih.gov/pubmed/20338284

“Reduced consumption of trans-fatty acids (TFA) is desirable to lower coronary heart disease (CHD) risk.”

European Journal Of Clinical Nutrition • May 2009

Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils

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Abstract

BACKGROUND/OBJECTIVES

Reduced consumption of trans-fatty acids (TFA) is desirable to lower coronary heart disease (CHD) risk. In practice, partially hydrogenated vegetable oils (PHVO) that contain both TFAs and other fatty acids are the unit of replacement and could be replaced with diverse alternative fats and oils. We performed quantitative estimates of CHD effects if a person’s PHVO consumption were to be replaced with alternative fats and oils based on (1) randomized dietary trials and (2) prospective observational studies.

SUBJECTS/METHODS

We performed meta-analyses of (1) the effects of TFAs on blood lipids and lipoproteins in controlled dietary trials and (2) associations of habitual TFA consumption with CHD outcomes in prospective cohort studies. On the basis of these results and corresponding findings for saturated fatty acids (SFA), cis-monounsaturated fatty acids (MUFA) and cis-polyunsaturated fatty acids (PUFA), we calculated the effects on CHD risk for replacing 7.5% of energy from three different PHVO formulations (containing 20, 35 or 45% TFAs) with butter, lard, palm or vegetable oils.

RESULTS

In controlled trials, each 1% energy replacement of TFAs with SFAs, MUFAs or PUFAs, respectively, decreased the total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio by 0.31, 0.54 and 0.67; the apolipoprotein (Apo)-B/ApoAI ratio by 0.007, 0.010 and 0.011; and lipoprotein (Lp)(a) by 3.76, 1.39 and 1.11 mg/l ($P<0.05$ for each). We also included possible effects on C-reactive protein (CRP) of TFAs vs other fats from one trial. On the basis of these risk factor changes in controlled trials, CHD risk would be variably decreased by different fats and oils replacing 7.5% of energy from 20% TFA PHVO (CHD risk reduction: -2.7% (butter) to -9.9% (canola)); 35% TFA PHVO (-11.9% (butter) to -16.0% (canola)); or 45% TFA PHVO (-17.6% (butter) to -19.8% (canola)). In prospective cohort studies, each 2% energy replacement of TFAs with SFAs, MUFAs or PUFAs would lower CHD risk by 17% (95% confidence interval (CI)=7-25%), 21% (95% CI=12-30%) or 24% (95% CI=15-33%), respectively. On the basis of these associations in observational studies, CHD risk would be variably decreased by different fats and oils replacing 7.5% of energy from 20% TFA PHVO (CHD risk reduction: +0.5% (butter) to -21.8% (soybean)); 35% TFA PHVO (-14.4% (butter) to -33.4% (soybean)); or 45% TFA PHVO (-22.4% (butter) to -39.6% (soybean)). The demonstrated effects on TC/HDL-C, ApoB/ApoAI, Lp(a), and CRP in randomized feeding trials together accounted for approximately 65-80% and approximately 50% of the estimated risk reduction for replacing PHVO with animal fats and vegetable oils, respectively, that would be calculated from prospective cohort studies.

CONCLUSIONS

Effects on CHD risk of removing PHVO from a person’s diet vary depending on the TFA content of the PHVO and the fatty acid composition of the replacement fat or oil, with direct implications for reformulation of individual food products. Accounting for the summed effects of TFAs on multiple CHD risk factors provides more accurate estimates of potential risk reduction than considering each risk factor in isolation, and approaches the estimated risk reduction derived from prospective cohort studies.

http://www.ncbi.nlm.nih.gov/pubmed/19424216

Histological Histopathology • September 2009

Voluntary oral feeding of rats not requiring a very high fat diet is a clinically relevant animal model of non-alcoholic fatty liver disease (NAFLD)

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Abstract

Animal models used to study the pathogenesis of non-alcoholic fatty liver disease (NAFLD) are, in general, either genetically altered, or fed with a diet that is extremely high in fat or carbohydrates. Recent findings support the role of oxidative stress, lipid peroxidation and inflammation as probable causative factors. We hypothesize that not only the amount of dietary fat, but the quality of fat is also important in inducing NAFLD. Based on previous observations that female rats fed a diet comprising unsaturated fatty acids are susceptible to liver injury, we proposed that female rats fed with a diet containing fish oil and dextrose would develop pathological and biochemical features of NAFLD. We fed a highly unsaturated fat diet (30% fish oil) to female Sprague-Dawley rats (180-200g), consumed ad libitum for 8 weeks (NAFLD; n=6-8). Control animals (CF; n=6-8) were fed with an isocaloric regular rat chow. At killing, blood and liver samples were collected for serum alanine aminotransferase (ALT), histology and molecular analysis. Each histological sample was evaluated for fatty liver (graded from 0 to 4+ according to the amount of fatty change), necrosis (number of necrotic foci (no./mm2) and inflammation (cells per mm2). The amount of collagen formation was estimated based on the amount of Sirius Red staining. Reverse transcriptase polymerase chain reaction (RT-PCR) was carried out for tumor necrosis factor alpha (TNF-alpha), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), adiponectin, glutathione peroxidase (GPx), superoxide dismutase (Cu/Zn SOD) and catalase (CAT). Western Blot analysis was done for cyclooxygenases-2 (COX-2), inducible nitric oxide synthase (iNOS) and nitrotyrosine. Electrophoretic mobility shift assay was performed for nuclear factor-kappa B (NF-kB) activity. NAFLD rats had a significantly higher serum ALT level, amount of collagen formation, fatty liver, necrosis and inflammation when compared with the chow-fed control rats. mRNA and protein levels of NF-kB regulated genes, which included TNF-alpha, COX-2 and iNOS were also significantly ($p<0.01$; $p<0.01$; $p<0.05$ respectively) upregulated in the NAFLD group when compared with the chow-fed control rats. mRNA levels of antioxidants CAT and GPX were reduced by 35% and 50% respectively in the NAFLD group. However, Cu/Zn SOD mRNA was similar in both groups. The mRNA level of adiponectin was also reduced in NAFLD group. NF-kB activity was markedly increased in the NAFLD rats ($p<0.01$). The level of oxidative stress, represented by the formation of nitrotyrosine, was significantly elevated in the NAFLD rats ($p<0.01$). We conclude that NAFLD rats demonstrated several features of NAFLD, which included fatty liver, inflammation, necrosis, increased oxidative stress, an imbalance between pro and antioxidant enzymes mRNAs, reduced adiponectin levels and upregulation of pro-inflammatory mediators. We propose that female rats fed with a diet containing highly unsaturated fatty acids are an extremely useful model for the study of NAFLD.

“We propose that female rats fed with a diet containing highly unsaturated fatty acids are an extremely useful model for the study of **Non-Alcoholic Fatty Liver Disease.**”

http://www.ncbi.nlm.nih.gov/pubmed/19609863

“Higher intakes of partially hydrogenated vegetable oils are associated with **elevated concentrations of inflammatory biomarkers**, whereas higher intakes of non-hydrogenated vegetable oils are associated with **lower plasma concentrations of these biomarkers.**”

American Journal Of Clinical Nutrition • October 2008

Home use of vegetable oils, markers of systemic inflammation, and endothelial dysfunction among women

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Abstract

BACKGROUND

Most knowledge about adverse health effects of trans fats was mainly derived from studies done in Western populations of European or American origins; few data are available in the understudied region of the Middle East.

OBJECTIVE

We assessed the association between consumption of partially hydrogenated vegetable oils (PHVOs) and non-HVOs and circulating concentrations of inflammatory markers among Tehrani women aged 40-60 y.

RESULTS

The energy-adjusted daily intakes (mean +/- SD) of PHVOs and non-HVOs were 23 +/- 11 and 22 +/- 10 g/d, respectively. After control for potential confounders, women in the highest quintile of PHVO intake had higher plasma concentrations of C-reactive protein (CRP; percentage difference from lowest quintile: 45%; P for trend: <0.01), tumor necrosis factor-alpha (TNF-alpha; 66%; P for trend: <0.01), interleukin-6 (72%; P for trend: <0.05), and soluble intercellular adhesion molecule-1 (sICAM-1; 22%; P for trend: <0.01) than did women in the lowest quintile. In contrast, higher consumption of non-HVOs was associated with lower circulating concentrations of CRP (percentage difference between top and bottom quintiles: -23%; P for trend: 0.05), TNF-alpha (-29%; P for trend: <0.01), serum amyloid A (-24%; P for trend: <0.01), and sICAM-1 (-19%; P for trend:<0.05). Adjustment for body mass index, fasting plasma glucose, and lipid profiles slightly attenuated the associations in some cases.

CONCLUSIONS

Higher intakes of PHVOs are associated with elevated concentrations of inflammatory biomarkers, whereas higher intakes of non-HVOs are associated with lower plasma concentrations of these biomarkers.

Full text with references

http://ajcn.nutrition.org/content/88/4/913.long

“Intake of Trans Fatty Acids is high in Iranian homes and contributes to a sizeable proportion of Coronary Heart Disease events. Replacement of partially hydrogenated oils with unhydrogenated oils would likely produce substantial reductions in Coronary Heart Disease incidence.”

European Journal Of Clinical Nutrition • August 2007

Consumption of trans fats and estimated effects on coronary heart disease in Iran

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Abstract

OBJECTIVE

To investigate the consumption of industrial trans-fatty acids (TFAs) in Iranian homes and the proportion of coronary heart disease (CHD) events in Iran attributable to such intake.

DESIGN, SETTING AND PARTICIPANTS

The consumption of industrial TFAs was determined using (1) detailed in-home assessments of dietary intake among 7158 urban and rural households containing 35 924 individuals and (2) gas chromatography to determine TFA contents of the most commonly consumed partially hydrogenated oils. The population-attributable risk for CHD owing to TFA consumption was calculated on the basis of (1) documented effects of TFAs on total:high-density lipoprotein (HDL) cholesterol in randomized controlled dietary trials and (2) relationships of TFA intake with incidence of CHD in prospective observational studies.

RESULTS

Partially hydrogenated oils were used extensively for cooking in Iranian homes with average per-person intake of 14 g/1000 kcal. TFAs accounted for 33% of fatty acids in these products, or 4.2% of all calories consumed (12.3 g/day). On the basis of total:HDL cholesterol effects alone, 9% of CHD events would be prevented by replacement of TFA in Iranian homes with cis-unsaturated fats (8% by replacement with saturated fats). On the basis of relationships of TFA intake with CHD incidence in prospective studies, 39% of CHD events would be prevented by replacement of TFA with cis-unsaturated fats (31% by replacement with saturated fats). These population-attributable risks may be overestimates owing to competing risks and because not all the fat used for cooking might actually be consumed. If actual TFA consumption were only half as large, the estimated proportion of CHD events prevented by TFA elimination would be 5% on the basis of total:HDL cholesterol effects and replacement with cis-unsaturated (4% for replacement with saturated fats), and 22% on the basis of prospective studies and replacement with cis-unsaturated fats (17% for replacement with saturated fats). These estimates do not include possible additional benefits derived from replacing TFAs with vegetable oils containing n-3 fatty acids.

CONCLUSIONS

Intake of TFAs is high in Iranian homes and contributes to a sizeable proportion of CHD events. Replacement of partially hydrogenated oils with unhydrogenated oils would likely produce substantial reductions in CHD incidence.

http://www.ncbi.nlm.nih.gov/pubmed/17268422

CHAPTER TWO

The Mediterranean Diet vs The American Diet

The Peer Review

A Western diet is described as a diet with inadequate fruits, vegetables, whole grains, legumes, fish, and low-fat dairy products and excessive amounts of refined and processed foods, alcohol, salt, red meats, sugary beverages, snacks, eggs, and butter. The Western diet, which is low in potassium, high in sodium, fats, and simple carbohydrates, has been implicated in many diseases, including atherosclerosis, type II diabetes, hypertension, and obesity. The truth is, our western diet can be implicated in almost every disease known to humankind starting with the propensity for inflammation.

A new British study provides further evidence that eating a so-called "Western" diet may not be good for you in the long run. People who eat this kind of diet—which includes fried and sweet foods, processed and red meat, refined grains and high-fat dairy products—are at increased risk for premature death. And those who do make it to old age are less likely to be in good health when they get there.

The study included nearly 3,800 men and 1,600 women in Britain, with an average age of fifty-one, who were followed from 1985 to 2009. By the end of that time, 73 percent of the participants had experienced normal aging and 4 percent had undergone ideal aging, which is defined as free of chronic conditions with high scores on tests of physical and mental abilities. During the follow-up period, 13 percent of the participants had a nonfatal cardiovascular event, 3 percent died from heart-related causes and 7 percent died from other causes, according to the research, which was published in The American Journal of Medicine.

Those who ate a Western style diet were less likely to have ideal aging, lead investigator Tasnime Akbaraly of INSERM, a biomedical and public health research institution in Montpelier, France, said in a journal news release. "We showed that following specific dietary recommendations ... may be useful in reducing the risk of unhealthy aging, while avoidance of the Western-type foods might actually improve the possibility of achieving older ages free of chronic diseases and remaining highly functional," Akbaraly said.

This chapter and all of the others simply confirm that we're marks and we've been shaken down and fleeced. We've been televisoned into believing that the MacBurger patties, fries and shakes, the "American Way" of processed foods in bags, boxes and cans, white bread, white flour, white sugar and white salt won't harm us when in fact these nutrition-free foods don't even approximate what we would or should actually refer to as food—and they kill. The average American diet lacks fresh fruit, vegetables, nuts, seeds, berries, herbs and spices, has the wrong oils, the wrong fats, the wrong sugars, the wrong salts and the really wrong chemical additives that will, all together and without question, eventually make you deathly ill. Yet what we also have is a population that largely knows not one iota about what they put in their mouths or the mouths of their offspring. And isn't it revealing that the same companies that monopolize the additives, preservatives, colors and other food drugs in the marketplace are ultimately owned by many of the same shareholders that make the medications we require to stay alive after eating these food poisons for decades.

It's a trillion dollar global drug racket.

“Our findings suggest that adherence to the Western pattern is potentially an unfavorable indicator of **asthenozoospermia risk**.”

Journal Of The American College Of Nutrition • January 2016

Adherence to the Western Pattern Is Potentially an Unfavorable Indicator of Asthenozoospermia Risk: A Case-Control Study

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Abstract

OBJECTIVE:

The aim of this case-control study was to examine the relationship between dietary patterns and asthenozoospermia risk.

METHODS

In total, 107 incident asthenozoospermic men and 235 age-matched controls were interviewed through the infertility clinics in Tehran, Iran, from January 2012 to November 2013. Usual dietary intakes were collected using a semiquantitative food frequency questionnaire and semen quality data were analyzed according to the fifth edition of the World Health Organization (WHO) guidelines. Dietary patterns were derived using factor analysis. The first tertile served as the reference category for regression analyses.

RESULTS

In principal component analysis, 2 dietary patterns emerged: a "prudent pattern" (leafy green vegetables, yellow vegetables, other vegetables, tomatoes, fish and other seafood, fruits and natural fruit juices, legumes, whole grains, poultry, tea and coffee, low-fat dairy products, and vegetable oils) and a "Western pattern" (organ meats, red and processed meats, sugar, soft drinks and confectionary, pasta, rice and refined grains, potatoes, french fries and fast foods, high-fat dairy products, hydrogenated fats, mayonnaise and fatty sauces, and snacks). After adjustment for potential confounders, participants in the highest tertile of the prudent pattern scores had 54% lower risk of asthenozoospermia compared to those in the lowest (p for trend: 0.003). Being in the highest tertile of the Western pattern was positively associated with asthenozoospermia risk (odds ratio [OR] = 2.86; 95% confidence interval [CI], 1.83-2.97).

CONCLUSIONS

Our findings suggest that adherence to the Western pattern is potentially an unfavorable indicator of asthenozoospermia risk and a diet composed mainly of plant-based foods may be associated with a reduced risk.

http://www.ncbi.nlm.nih.gov/pubmed/25764357

ASTHENOZOOSPERMIA

Asthenozoospermia (or asthenospermia) is the medical term for reduced sperm motility. Complete asthenozoospermia, that is, 100% immotile spermatozoa in the ejaculate, is reported at a frequency of 1 of 5000 men. It decreases the sperm quality and is therefore one of the major causes of infertility or reduced fertility in men. Causes of complete asthenozoospermia include metabolic deficiencies, ultrastructural abnormalities of the sperm flagellum and, as you'll see, our western diet.

METABOLIC SYNDROME

Metabolic syndrome is a disorder of energy utilization and storage, diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density cholesterol (HDL) levels.

Metabolic syndrome increases the risk of developing cardiovascular disease, particularly heart failure, and diabetes. Some studies have shown the prevalence in the USA to be an estimated 34% of the adult population, and the prevalence increases with age.

Metabolic syndrome is also known as metabolic syndrome X, cardiometabolic syndrome, syndrome X, insulin resistance syndrome, Reaven's syndrome (named for Gerald Reaven), and CHAOS (in Australia).

Clinical Nutrition • March 2016

Combined effect of diet and cervical microbiome on the risk of cervical intraepithelial neoplasia

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Abstract

BACKGROUND & AIMS

Several food groups or dietary factors and the cervical microbiota may be involved in cervical carcinogenesis, but the evidence is not clear yet. We aimed to assess the association between dietary pattern and cervical intraepithelial neoplasia (CIN) and the combined effect of dietary pattern and cervical microbiome on the risk of CIN.

METHODS

The cervical microbiota and diet assessed by pyrosequencing and a food-frequency questionnaire, respectively, of 65 women with CIN and 72 control women were used in this study. Principal component analysis and cluster analysis were used to identify dietary patterns and microbiome community types, respectively. The association between dietary pattern and CIN risk was assessed using multivariable logistic regression analysis. The combined effect of dietary pattern and microbiome on CIN risk was determined using relative excess risk due to interaction (RERI) and synergy index (S).

RESULTS

Two dietary patterns and four community types were identified: prudent diet characterized by higher intake of vegetables and fishes; semi-Western diet characterized by higher intake of bread, dairy products, eggs, and soft drinks and relatively higher fat intake ratio; and Lactobacillus crispatus-, L. iners-, Atopobium vaginae-, and Prevotella bivia-dominant types. The high-scoring group of participants with a semi-Western diet had a higher risk of CIN (odds ratio [OR] 3.44, 95% confidence interval [CI] 1.11-10.7, p = 0.03), compared with the low or medium-scoring group of those with a semi-Western diet. L. iners-dominant (OR 6.39, 95% CI 1.52-26.7, p = 0.01) and A. vaginae-dominant (OR 4.99, 95% CI 1.17-21.3, p = 0.03) dominant types had a higher risk of CIN, compared with the L. crispatus-dominant type. The synergistic effect of semi-Western diet and A. vaginae-dominant type on CIN risk was observed (OR 20.8, 95% CI 2.21-195.6, p = 0.01, RERI/S 9.64/1.96).

CONCLUSIONS

Our findings suggest that semi-Western diet and its combination with A. vaginae-dominant microflora may represent an important risk factor for cervical neoplasia.

http://www.ncbi.nlm.nih.gov/pubmed/27075319

Presse Medical • May 2016

Food addiction: Definition, measurement and limits of the concept, associated factors, therapeutic and clinical implications

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Abstract

Addictions, which are characterized by the inability to control a behavior despite existence of physical or psychological consequences, have biological, psychological and social determinants. Although the possibility of developing an addiction to some psychoactive substances (e.g. alcohol, tobacco, cannabis) and to gambling (i.e., gambling disorder) is now well demonstrated, the possibility to develop a non-drug addiction (i.e., behavioral addiction) to certain behaviors which provide pleasure (e.g. eating, having sex, buying things) is still in debate. The concept of food addiction, which refers to people who exhibit substance dependence criteria in relation to some high-fat and high-sugar foods, was recently proposed by applying substance dependence DSM criteria to eating behavior. To assess food addiction, the Yale Food Addiction Scale is now the only self-administered questionnaire (diagnosis and estimate of the number of symptoms of food addiction). Prevalence for food addiction is higher in overweight and obese patients, and in patients with certain psychopathological characteristics (i.e., depression, Attention Deficit Hyperactivity Disorder, high impulsivity), in patients who are single and in patients with neurobiological alterations in the reward system. However, it is still unclear whether food addiction is necessary associated with subsequent increase in body weight and/or obesity. An increasing number of studies demonstrated that drug addiction and food addiction shares some similar clinical, neurobiological and psychopathological and sociocultural risk factors. To test the pertinence to include food addiction as an addiction, it would be interesting to conduct future studies in patients who may experience harms related to their food addiction, including not only patients with obesity, but also patients with metabolic syndrome, type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, stroke, or coronary heart disease. Food addiction is a clinical and multidimensional concept which requires integrated care with psychotherapy, pharmacological and social lines of approach. This concept has also practical implications in terms of prevention and public health (e.g., prevention, brief interventions, possible law enforcement regarding some kinds of food which could present some addictive properties).

http://www.ncbi.nlm.nih.gov/pubmed/27211587

“In this study we documented that adherence to the Mediterranean diet may accrue benefits **up to 2 years of longer survival.**”

European Journal Of Epidemiology • May 2016

Quantifying the benefits of Mediterranean diet in terms of survival

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Abstract

Beneficial effects of Mediterranean diet (MD) have been consistently documented. However, to fully understand the public health implications of MD adherence, an informative step is to quantify these effects in terms of survival time differences. The aim of this study was to evaluate the impact of MD on survival, presenting results in terms of differences in median age at death. We used data from 71,333 participants from a large population-based cohort of Swedish men and women, followed-up between January 1, 1998, and December 31, 2012. A total score of MD, ranging from 0 to 8, was calculated by including information on vegetables and fruits consumption, legumes and nuts, non-refined/high fiber grains, fermented dairy products, fish, red meat, use of olive oil/rapeseed oil, and moderate alcohol intake. Multivariable-adjusted differences in median age at death were estimated with Laplace regression and presented as a function of the MD score. During 15 years of follow-up we documented 14,697 deaths. We observed a linear dose-response association between the MD score and median age at death, with higher score associated with longer survival. The difference in median age at death between participants with the extreme scores (0 vs 8) of MD was up to 2 years (23 months, 95 % CI: 16-29). In this study we documented that adherence to MD may accrue benefits up to 2 years of longer survival.

http://www.ncbi.nlm.nih.gov/pubmed/26848763

“We conclude that higher adherence to a Mediterranean-like diet is associated with lower risk of future hip fracture.”

Journal Of Bone And Mineral Research • June 2016

Mediterranean Diet and Hip Fracture in Swedish Men and Women

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Abstract

A Mediterranean diet, known to have beneficial effects on cardiovascular health, may also influence the risk of hip fracture although previous studies present discrepant results. We therefore aimed to determine whether the rate of hip fracture was associated with degree of adherence to a Mediterranean diet. We combined two Swedish cohort studies consisting of 37,903 men and 33,403 women (total n=71,333, mean age 60 years) free of previous cardiovascular disease and cancer who answered a medical and a food-frequency questionnaire in 1997. A modified Mediterranean diet score (mMED; range 0-8 points) was created based on high consumption of fruits and vegetables, legumes and nuts, whole grains, fermented dairy products, fish, and olive/rapeseed oil, moderate intake of alcohol, and low intake of red and processed meat. Incident hip fractures between 1 January 1998 and 31 December 2012 were retrieved from the National Patient Register. Hazard ratios (HR) and 95% confidence intervals (CI) adjusted for potential confounders were calculated using Cox proportional hazards regression. Differences in age at hip fracture were calculated using multivariable Laplace regression. During follow-up, 3,175 hip fractures occurred at a median age of 73.3 years. One unit increase in the mMED was associated with 6% lower hip fracture rate (adjusted HR=0.94; 95% CI 0.92-0.96) and with a three months higher median age at hip fracture (50th percentile difference=2.8 months; 95% CI 1.4-4.2). Comparing the highest quintile of adherence to the mMED (6-8 points) with the lowest (0-2 points) conferred an adjusted HR of hip fracture of 0.78 (95% CI 0.69-0.89) and a 12 months higher median age of hip fracture (50th percentile difference=11.6 months; 95% CI 4.2-19.0). Results were similar in men and women. We conclude that higher adherence to a Mediterranean-like diet is associated with lower risk of future hip fracture.

http://www.ncbi.nlm.nih.gov/pubmed/27345330

“Palm oil consumption results in higher LDL cholesterol than do vegetable oils low in saturated fat and higher HDL cholesterol than do trans fat-containing oils in humans. The effects of palm oil on blood lipids are as expected on the basis of its high saturated fat content, **which supports the reduction in palm oil use by replacement with vegetable oils low in saturated and trans fat.”**

Journal Of Nutrition • July 2015

Palm Oil Consumption Increases LDL Cholesterol Compared with Vegetable Oils Low in Saturated Fat in a Meta-Analysis of Clinical Trials

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Abstract

BACKGROUND

Palm oil contains a high amount of saturated fat compared with most other vegetable oils, but studies have reported inconsistent effects of palm oil on blood lipids.

OBJECTIVE

We systematically reviewed the effect of palm oil consumption on blood lipids compared with other cooking oils using data from clinical trials.

METHODS

We searched PubMed and the Cochrane Library for trials of at least 2 wk duration that compared the effects of palm oil consumption with any of the predefined comparison oils: vegetable oils low in saturated fat, trans fat-containing partially hydrogenated vegetable oils, and animal fats. Data were pooled by using random-effects meta-analysis.

RESULTS

Palm oil significantly increased LDL cholesterol by 0.24 mmol/L (95% CI: 0.13, 0.35 mmol/L; I(2) = 83.2%) compared with vegetable oils low in saturated fat. This effect was observed in randomized trials (0.31 mmol/L; 95% CI: 0.20, 0.42 mmol/L) but not in nonrandomized trials (0.03 mmol/L; 95% CI: -0.15, 0.20 mmol/L; P-difference = 0.02). Among randomized trials, only modest heterogeneity in study results remained after considering the test oil dose and the comparison oil type (I(2) = 27.5%). Palm oil increased HDL cholesterol by 0.02 mmol/L (95% CI: 0.01, 0.04 mmol/L; I(2) = 49.8%) compared with vegetable oils low in saturated fat and by 0.09 mmol/L (95% CI: 0.06, 0.11 mmol/L; I(2) = 47.8%) compared with trans fat-containing oils.

CONCLUSIONS

Palm oil consumption results in higher LDL cholesterol than do vegetable oils low in saturated fat and higher HDL cholesterol than do trans fat-containing oils in humans. The effects of palm oil on blood lipids are as expected on the basis of its high saturated fat content, which supports the reduction in palm oil use by replacement with vegetable oils low in saturated and trans fat. This systematic review was registered with the PROSPERO registry at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002601#.VU3wvSGeDRZ as CRD42012002601.

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Inflammaging and cancer:
[INFLAMMAGING: a state of chronic, low-level, systemic inflammation]
a challenge for the Mediterranean diet

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[see next page]

INFLAMMAGING

Abstract

“Aging is considered the major risk factor for cancer, one of the most important mortality causes in the western world. **Inflammaging, a state of chronic, low-level systemic inflammation, is a pervasive feature of human aging. Chronic inflammation increases cancer risk and affects all cancer stages, triggering the initial genetic mutation or epigenetic mechanism, promoting cancer initiation, progression and metastatic diffusion.** Thus, inflammaging is a strong candidate to connect age and cancer. A corollary of this hypothesis is that interventions aiming to decrease inflammaging should protect against cancer, as well as most/all age-related diseases. Epidemiological data are concordant in suggesting that the Mediterranean Diet (MD) decreases the risk of a variety of cancers but the underpinning mechanism(s) is (are) still unclear. Here we review data indicating that the MD (as a whole diet or single bioactive nutrients typical of the MD) modulates multiple interconnected processes involved in carcinogenesis and inflammatory response such as free radical production, NF-aB activation and expression of inflammatory mediators, and the eicosanoids pathway. Particular attention is devoted to the capability of MD to affect the balance between pro- and anti-inflammaging as well as to emerging topics such as maintenance of gut microbiota (GM) homeostasis and epigenetic modulation of oncogenesis through specific microRNAs.”

Full text, charts, graphs and 221 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425163/

“In this narrative review, we consider the mechanistic and epidemiological evidence that food processing influences phytochemicals in selected food groups in the Mediterranean diet (olives, olive oil, vegetables and nuts), and that this influences the protective effects of these foods against chronic diseases associated with inflammation. We also examine how the pro-inflammatory properties of meat consumption can be modified by Mediterranean cuisine.”

Nutrients • September 2015

Food Processing and the Mediterranean Diet

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Abstract

The benefits of the Mediterranean diet (MD) for protecting against chronic disorders such as cardiovascular disease are usually attributed to high consumption of certain food groups such as vegetables, and low consumption of other food groups such as meat. The influence of food processing techniques such as food preparation and cooking on the nutrient composition and nutritional value of these foods is not generally taken into consideration. In this narrative review, we consider the mechanistic and epidemiological evidence that food processing influences phytochemicals in selected food groups in the MD (olives, olive oil, vegetables and nuts), and that this influences the protective effects of these foods against chronic diseases associated with inflammation. We also examine how the pro-inflammatory properties of meat consumption can be modified by Mediterranean cuisine. We conclude by discussing whether food processing should be given greater consideration, both when recommending a MD to the consumer and when evaluating its health properties.

Full text with 249 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586566/

"The manuscript reviews the impacts and mechanisms of harm for our over-indulgence in sugar, salt, and fat, as well as the data outlining the impacts of artificial sweeteners, gluten, and genetically modified foods ... today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet **may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.**"

Nutrition Journal • June 2014

Fast food fever: reviewing the impacts of the Western diet on immunity

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Abstract

While numerous changes in human lifestyle constitute modern life, our diet has been gaining attention as a potential contributor to the increase in immune-mediated diseases. The Western diet is characterized by an over consumption and reduced variety of refined sugars, salt, and saturated fat. Herein our objective is to detail the mechanisms for the Western diet's impact on immune function. The manuscript reviews the impacts and mechanisms of harm for our over-indulgence in sugar, salt, and fat, as well as the data outlining the impacts of artificial sweeteners, gluten, and genetically modified foods; attention is given to revealing where the literature on the immune impacts of macronutrients is limited to either animal or in vitro models versus where human trials exist. Detailed attention is given to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.

Full text, graphs, charts and 246 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074336/

McDONALD'S GLOBAL FOOTPRINT

American multinational corporations, and calling them 'American' is an absurdity, have successfully exported an extraordinary American product. So successfully in fact that the same diseases we Americans have become used to and complacent about, and which diseases are rising at exponential rates, are now rising across the globe as well.

We'll use McDonald's as an example because it's the largest chain of fast food restaurants in the world. It has more than 35,000 outlets worldwide and the majority of McDonald's outlets outside of the United States are franchises as opposed to private business owners here in the US.

Here are some of the statistics regarding the McDonalds business model. Think about this overwhelmingly cheap and deficient diet as the perfect export model for corporate shareholder profit which is in no short supply—net income in 2014, after operating expenses on gross sales of 27.4 billion was 4.75 billion. With assets of 34.2 billion, equity of 12.8 billion and 420,000 employees, McDonalds and the other 25+ highly successful fast food purveyors of cheap, additive laden, disease and disorder causing foods have successfully exported the American diet as a powerful global business model. No different than Walmart or anyone else of course, but this export comes with definite, scientifically proven disease and disorder in thousands of peer reviewed reports on these "food" ingredients. Food in quotes because they serve anything and everything except what's commonly known as food.

Why? Many reasons. TV and print advertising through the 50s, 60s and 70s helped. The breakthrough globalist concept of 'Women's Rights' aided and abetted the business model since today most women work and as a result we all have little time to sit down for a leisurely, home-cooked, farm-fresh family meal. Now our lives are hurried and we lack not only time but we're short on money too. Fast food, Take-Out, microwaveable Hungry-Man dinners and boxed or prepackaged lunches all fit this new paradigm like a glove.

COUNTRY	OPERATING OUTLETS
US	14,267
Canada	1,427
Puerto Rico	108
US Virgin Islands	6
Costa Rica	54
Australia	920
Guam	5
Japan	2,975
Netherlands	236
Panama	57
Germany	1,477
France	1,300+
El Salvador	13
Sweden	230
Guatemala	76
Curacao	5
United Kingdom	1,240
Hong Kong	237
Bahamas	3
New Zealand	162
Switzerland	157
Ireland	84
Austria	189
Belgium	67
Brazil	812
Singapore	125
Spain	493
Denmark	89
Philippines	400+
Malaysia	314
Norway	74
Taiwan	413
Andorra	4
Finland	83
Thailand	225
Aruba	3
Luxembourg	9
Venezuela	140
Italy	530+
Mexico	402
Cuba	1
Turkey	230+
Argentina	209
Macau (China)	27
Serbia	23
South Korea	415
Hungary	100
Russia	510
China (mainland)	2,000+
Chile	77
Indonesia	160
Portugal	151
Greece	22
Uruguay	21
Czech Republic	94
Poland	359
Monaco	4
Brunei	1
Morocco	37
Northern Marianas	2
Israel	180
Slovenia	16
Saudi Arabia	224
Kuwait	75
New Caledonia	2
Oman	15
Egypt	72
Bulgaria	42
Bahrain	17
Latvia	12
United Arab Emirates	114
Estonia	10
Romania	68
Malta	8
Colombia	81
Slovakia	30
South Africa	200+
Qatar	25
Honduras	8
Saint Maarten	3
Croatia	25
Samoa	1
Fiji Islands	3
Liechtenstein	3
Lithuania	11
Cyprus	18
India	250+
Peru	40
Jordan	24
Paraguay	11
Dominican Republic	31
French Polynesia	6
Belarus	8
Ukraine	76
Jersey	1
Ecuador	27
Isle Of Man	1
Suriname	2
Moldova	6
Nicaragua	6
Lebanon	33
Pakistan	33
Sri Lanka	7
Georgia	9
San Marino	1
Gibraltar	1
Azerbaijan	11
American Samoa	2
Mauritius	3
Iraq	1
Bonia/Herzegovia	5
Trinidad & Tobago	6
Tunisia	1
Namibia	2
Kazakhstan	5

Fast Food Fever has never been stronger than it is in America today and it's obviously catching on globally but there's still no international match for America's desire for processed Fast Food.

American Journal Of Clinical Nutrition • July 2014

Meat, dairy, and cancer

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Abstract

"In 2007 the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) report judged that the evidence for an association between red and processed meat consumption and colorectal cancer was convincing. In addition, the effect of other animal products on cancer risk has been studied, and the WCRF/AICR report concluded that milk probably decreases the risk of colorectal cancer but diets high in calcium probably increase the risk of prostate cancer, whereas there was limited evidence for an association between milk and bladder cancer and insufficient evidence for other cancers. There are several potential mechanisms relating meat to cancer, including heterocyclic amines, polycyclic aromatic hydrocarbons, N-nitroso compounds, and heme iron. Although the evidence in favor of a link between red and processed meat and colorectal cancer is convincing, the relations with other cancers are unclear. In this review, we summarize cohort studies conducted by the National Cancer Institute on meat and dairy intake in relation to cancer since the 2007 WCRF/AICR report. We also report the findings of meta-analyses published since 2007."

Full text, graphs, charts and 67 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4144110/

Nutrition Today • November 2015

Can Food Processing Enhance Cancer Protection?

John W. Erdman, Jr., Elizabeth Jeffery, Marc Hendrickx, Amanda J. Cross, and Johanna W. Lampe

INTRODUCTION

Food processing can be defined as the transformation of raw ingredients into food, or of food into other forms. This review summarizes an AICR symposium * that addressed the question of what is known about food processing in relation to cancer risk. To approach this question, it is valuable to understand something about the evolutionary history of food processing as well as the broad range of commonly utilized industrial/home processing technologies.

On the surface one might think that food processing is a modern application of technology to preserve food. Whereas our ancestors had little knowledge about microbial contamination and spoilage of food they figured out the utility of sun drying, fermentation and preservation with salt to extend their food supply to periods of need. For most of our forbearers, hunger was a daily challenge to overcome. In their classic textbook, Food Technology, Prescott and Proctor noted that "the growth of towns and cities involved larger need (for food) and new difficulties in storage and transportation....gradually transforming food production from an occupation to a business" (1). The foundations of the canning industry were developed by Appert in France in the early 19th century even before Pasteur began to elucidate the bases of microbiological spoilage of foods. With electricity came refrigeration and extension of shelf-life for perishable foods, followed by further shelf-life extension with development of frozen foods.

Today, modern food processing operations include some of the older technologies plus some newer ones. These include fermentation (with and without salt), dehydrations (sun, spray drying, freeze drying, hot air, etc.), freezing and cooling, many forms of thermal processing and various separation techniques (milling, membrane, centrifugation, etc.). There are many benefits from these techniques including protection from microbial and chemical hazards, availability of an array of foods year around, reduction of spoilage and of course convenience. Could there be drawbacks? Yes, of course, as one considers both the components of those foods (excess calories, salt, fat or sugar) or use of excess heat, whether the food is purchased from the manufacturer, a food service establishment or overheated on the grill at home, for example. On the other hand, some nutrients and health-promoting compounds may be more available after processing. This review paper will investigate both the potential benefits and the drawbacks to use of some types of food processing, specifically related to potential impact on cancer risk.

RETENTION AND BIOACCESSIBILITY OF BIOACTIVE FOOD COMPONENTS

Different processing procedures are used to convert raw materials into final food products that are acceptable for consumption and are easily digestible. For example, heating of vegetables can soften plant tissue and destroy naturally-occurring degradation enzymes but at the same time, excess heat can thermally degrade some important micronutrients. It is of crucial importance that micronutrients and bioactives (e.g. vitamin C, folates, carotenoids, anthocyanins, etc.) are both maximally retained during processing and storage and are maximally accessible during digestion (bioaccessible). The goal is to optimize nutrient uptake by the human body (bioavailability). The concern is the stability, and in some cases the chemical form, of highly bioaccessible water soluble micronutrients (e.g. vitamin C) or the stability, chemical form and accessibility to lipid soluble micronutrients (e.g., vitamin A) (2).

Water-soluble (hydrophilic) micronutrients

For water-soluble micronutrients, there are well documented examples of both positive and negative roles of processing: (i) the influence of processing conditions on maintaining vitamin C (e.g., protection against enzymatic degradation due to the presence of ascorbate oxidase, or oxidative and nonoxidative breakdown) highlighting the importance of processing – and even the sequence of processing steps (e.g. thermal processing prior to or after mechanical disintegration) and the presence of oxygen during processing; (ii) the enzymatic conversion of folates (from non-absorbed polyglutamate to bioavailable monoglutamate)

during processing due to the action of ß-conjugase (3) and (iii) maintaining conversion of glucosinolates to bioactive isothiocyanates during processing, due to protection of the active enzyme myrosinase in broccoli and other brassica.

Lipid-soluble (lipophilic) micronutrients

Carotenoids represent an interesting category of lipid-soluble micronutrients. Nutritional studies have shown that the mechanism of uptake follows the same digestive route as lipids and that carotenoids need to be incorporated into micelles within the gastrointestinal tract to facilitate absorption. This means that the processing of carotenoid-containing raw materials into foods for final incorporation of carotenoids into micelles during digestion should be designed to minimize barriers limiting this transfer.

The choice of raw materials and subsequent processing steps plays a key role in both the carotenoid profile at the moment of intake and the bioaccessibility later, during digestion. The raw materials create the starting point in terms of amount, physical state and type of carotenoids and their isomers. Mechanical processing (e.g. blending, high pressure homogenization (4)) will have an effect on the natural barriers to accessibility related to the chromoplast structure and the cell wall properties (5). Thermal processing may lead to possible carotenoid breakdown and isomerization (6) as well as changes in cell wall polysaccharides, in particular pectin changes. These concerted changes will lead to an overall balance of bioaccessible carotenoids (7). The addition of certain food ingredients, in particular lipids, during processing and/or digestion (8), can strongly influence the location of the carotenoids in the food matrix (e.g. transfer of carotenoids to the lipid phase and finally incorporation into micelles during digestion, which is necessary for optimal bioavailability). From these examples, it is clear that the interplay of raw materials, food ingredients, and processing become crucial factors influencing the amount, profile and bioaccessibility of carotenoids, and therefore the final health promoting effects of carotenoid-containing foods as part of our diet (9). The available information is far from complete but there is sufficient foundational knowledge for food technologists to fine tune processing parameters, maximizing the health benefit of carotenoid-containing food systems (10). This requires continuous dialogue between food technologists and nutritionists to deliver food systems with optimal health characteristics. Improved integration of these fields of expertise will allow targeted processing of foods for specific health-related functional properties.

PROCESSING OF CRUCIFERS TO RETAIN OPTIMAL BIOACTIVITY

Epidemiologic studies show that eating 3 – 5 servings of cruciferous vegetables per week can decrease risk for many different cancers, by 30 – 50% (11). Cruciferous vegetables contain a family of uniquely effective cancer preventive compounds termed glucosinolates. Although glucosinolates have no direct health effects, upon crushing or chewing cruciferous vegetables, such as broccoli, the glucosinolates come into contact with the plant enzyme myrosinase and release bioactive isothiocyanates, including sulforaphane. Heat processing, through industrial blanching before freezing or through home cooking, can destroy the myrosinase, so that we must rely on bacterial enzymes in the gut to release sulforaphane – but for most people, the gut only releases about 10% of the potential sulforaphane (12). If broccoli is steamed for 3 – 5 minutes, rather than boiled or microwaved, the enzyme is protected and sulforaphane is released for absorption (13).

An alternative option for ensuring that the enzyme is present in your meal is to include in the meal a second, uncooked, source of the enzyme such as stone-ground mustard, whole mustard seeds, coleslaw, red radish or arugula salad. Only a small amount of the raw vegetable is needed: Jeffery and co-workers added 0.25% by weight dried daikon radish to frozen broccoli that had been cooked in the microwave, and released 100% of the available sulforaphane (14). They carried out a small study showing that if men ate a processed broccoli product similar to a broccoli supplement, which had no myrosinase, very little sulforaphane was absorbed into their blood. In contrast, if they ate fresh broccoli sprouts, a substantial amount of sulforaphane was absorbed. Furthermore, when they ate the two products at the same meal, myrosinase from the sprouts was able to release sulforaphane from the powder that contained glucosinolates but no myrosinase (12).

If garlic is not crushed before cooking, heat processing inactivates alliinase enzymes, changing the flavor, limiting the production of bioactives and limiting the health benefits (15). We have grown accustomed to crushing garlic before cooking, which overcomes this. Until processors develop a way to protect myrosinase during cooking of broccoli, we need to learn to steam broccoli for only 3 or 4 minutes to protect the myrosinase enzyme until we crush/chew the cooked broccoli. Alternatively, we can add another source of the enzyme, an uncooked brassica, to the meal for full benefit of this cancer-fighting vegetable.

PROCESSING OF MEAT TO MINIMIZE FORMATION OF CARCINOGENS

Meat intake has been associated with an elevated risk of several chronic diseases, including cancers of the colorectum, stomach, esophagus, prostate, breast, and pancreas (16), as well as all-cause mortality (17). There are several plausible biological mechanisms potentially underlying an association between meat consumption and cancer, including components of meat or mutagens associated with meat preservation or preparation.

Meat preservation - processed meats

Curing meat by adding salt, nitrate, or nitrite or by smoking has been a method of preservation, or processing, for many years. Nitrate or nitrite is added to some processed meats as antibacterial agents and to produce the characteristic red-pink color of cured meats; however, they are also known precursors of N-nitroso compounds (NOCs), which can be formed within meat treated with nitrate or nitrite (17). NOCs are powerful chemical carcinogens and, therefore, even small amounts in the human body could be important. In addition, meat that is smoked is known to contain polycyclic aromatic hydrocarbons (PAHs), some of which are carcinogenic in animal models. An extensive review of the epidemiologic literature indicates that the evidence is “convincing” for a positive asso-

ciation between processed meat and colorectal cancer, and "probable" for salted fish and nasopharyngeal cancer (16). While there is limited evidence for a similar consensus for other cancers, numerous individual studies have identified positive associations between processed meat and cancers of the brain, oral cavity, larynx, pancreas, and prostate, for example. For specific processing procedures the evidence is limited but studies have also implicated salted meats and smoked meats in gastric cancer, as well as NOC intake from processed meats in colorectal cancer. Reducing any risks associated with processed meat involves limiting the consumption of this meat type. However, the formation of NOCs also can be reduced by the addition of ascorbic acid to the processing procedure, which is common practice in the U.S.

Meat preparation

In addition to processing procedures carried out before the meat reaches the consumer, the way meat is prepared at home may influence the associated risks. Meat that is cooked well-done by high-temperature cooking methods contains both heterocyclic amines (HCAs), as well as PAHs (19), both of which have shown carcinogenicity in animal models. Meat cooked well-done or by high-temperature cooking methods has been associated with an increased risk of cancers of the colorectum, lung, bladder, pancreas, and prostate.

Some epidemiologic studies have estimated individual HCA and PAH intake by linking detailed questionnaires with cooking information to a HCA and PAH database developed by the U.S. National Cancer Institute. Using this data, specific HCAs have been positively associated with cancer at several sites, including the colorectum, pancreas, and prostate. The formation of HCAs can be reduced by decreasing the heat and the length of cooking, or by pre-heating meat in the microwave, which removes the creatine needed for formation of HCAs to occur. In addition to being found in smoked foods, PAHs are formed in grilled/barbecued meat as the meat juices drip onto the hot fire, yielding flames containing a number of PAHs, which adhere to the surface of the meat. Epidemiologic studies of PAHs from meat in relation to cancer have reported increased risks of colorectal adenoma and pancreatic cancer.

In conclusion, meat can be a source of several carcinogens, depending on processing and preparation methods. Nevertheless, the intake of potential carcinogens from meat can be minimized if processed meat intake is limited and if meat is not cooked very well-done or by high-temperature cooking methods.

EFFECTS OF FERMENTATION OF FOODS

Fermentation is one of the oldest methods of food preservation and fermented foods are an important part of the diets of many populations worldwide. Nutritionally, fermentation can improve digestibility by hydrolyzing inedible components and can make inedible foods edible by metabolizing/ destroying anti-nutritional factors and toxins. Some fermented foods are also sources of live microbes introduced during the fermentation process. Pickling (i.e., fermenting in water with or without salt) is widely used to preserve vegetables. Several meta-analyses of studies in populations habitually consuming large amounts of pickled vegetables (e.g., Japan, Korea, China) suggest that high intakes of pickled vegetables may increase risk of esophageal and gastric cancer (20, 21) and fermented soy foods may increase gastric cancer risk (22). Cantonese-style salted fish, dried outdoors under lower than usual salt conditions and subject to fermentation, is a probable cause of nasopharyngeal cancer (23), although fish preserved by other pickling methods have not been associated with risk of this cancer. The association between pickled foods and risk of cancer has been attributed in part to the high levels of nitrate and nitrosamines generated during fermentation. These react to form carcinogenic NOCs, but formation can be slowed with vitamins C and E. Experimental studies in non-human primates suggest that Helicobacter pylori infection and NOCs in pickled foods may synergistically induce gastric cancer. Fermented dairy products containing live microbes (e.g., yogurt or cheeses such as camembert with a bloomy rind) may impart additional benefit beyond milk in relation to bladder cancer, at least in part due to the presence of lactic acid bacteria (24, 25).

Identifying the contribution of fermented foods in general or particular fermented foods specifically to cancer risk is challenging. Fermented foods as a group include a wide variety of foods. They are not consumed in isolation and cuisines high in some types of fermented foods also include other foods that may be considered healthy or less healthy. Future observational studies might benefit from distinguishing more explicitly between different types of fermented foods and more mechanistic studies are needed to follow up on epidemiologic findings.

CONCLUSIONS

This symposium addressed what is currently known about the benefits and drawbacks to some food processing procedures, specifically as processing techniques potentially impact cancer risk. There are many benefits to food processing, including protection from microbial and chemical hazards, availability of an array of foods year around, reduction of spoilage, improved digestibility and of course, convenience. Heating of foods is critical for protection against microbiological hazards such as pathogens and for enhancing the digestibility, bioaccessibility and bioavailability of nutrients and anti-carcinogens from foods. However, excessive heating may destroy some vitamins and bioactives particularly in fruits and vegetables or create carcinogens in meats. In order to reduce cancer risk, it is recommended, for example, that meats not be cooked well done or with very high temperatures.

To maximize the health benefits of certain foods, and to reduce the health risk of other foods, it is imperative that we continue to study the effects of processing and cooking

procedures whether the foods are processed by the food industry or prepared at home or in food service establishments. We have discussed the effects of heat processing on plant enzymes and the effect of high temperatures when cooking meat. In addition, preservation by some forms of fermentation or by the use of some additives, such as nitrate or nitrite, can lead to the formation of potentially carcinogenic compounds, whereas addition of other live bacteria to fermented products such as yogurt may support the gut in providing anticarcinogens to the body. Continuous dialogue between food technologists and nutritionists is necessary to deliver foods processed for optimal health.

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Original text

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“Eating addiction”, rather than “food addiction”, better captures addictive-like eating behavior

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Abstract

“Food addiction” has become a focus of interest for researchers attempting to explain certain processes and/or behaviors that may contribute to the development of obesity. Although the scientific discussion on “food addiction” is in its nascent stage, it has potentially important implications for treatment and prevention strategies. As such, it is important to critically reflect on the appropriateness of the term “food addiction”, which combines the concepts of “substance-based” and behavioral addiction. The currently available evidence for a substance-based food addiction is poor, partly because systematic clinical and translational studies are still at an early stage. We do however view both animal and existing human data as consistent with the existence of addictive eating behavior. Accordingly, we stress that similar to other behaviors eating can become an addiction in thus predisposed individuals under specific environmental circumstances. Here, we introduce current diagnostic and neurobiological concepts of substance-related and non-substance-related addictive disorders, and highlight the similarities and dissimilarities between addiction and overeating. We conclude that “food addiction” is a misnomer because of the ambiguous connotation of a substance-related phenomenon. We instead propose the term “eating addiction” to underscore the behavioral addiction to eating; future research should attempt to define the diagnostic criteria for an eating addiction, for which DSM-5 now offers an umbrella via the introduction on Non-Substance-Related Disorders within the category Substance-Related and Addictive Disorders.

Full text, PDF link with 149 references

http://www.sciencedirect.com/science/article/pii/S0149763414002140

Critical Reviews In Food Science And Nutrition • December 2014

Instant noodles: processing, quality, and nutritional aspects

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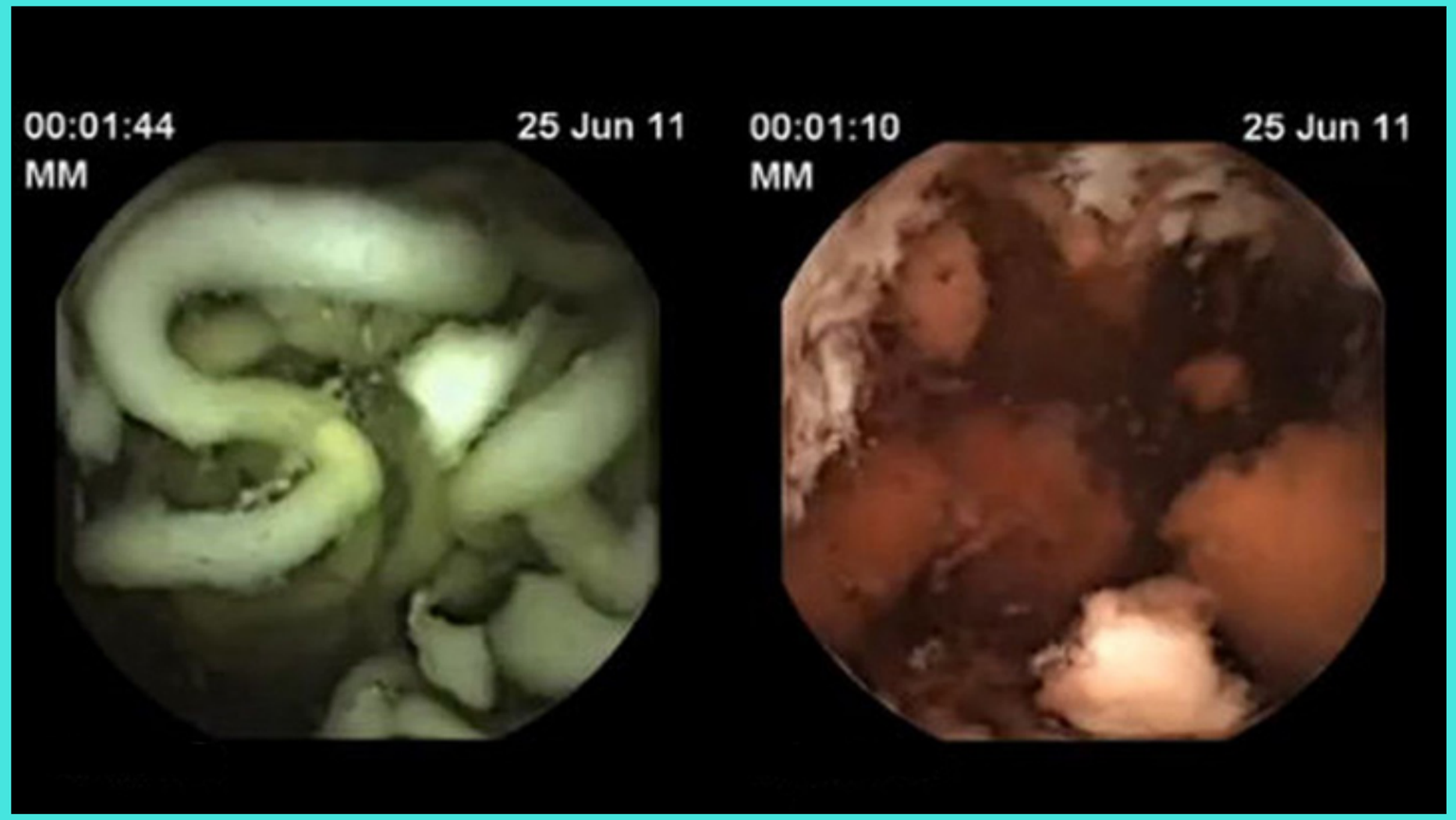
Abstract

Noodles are one of the staple foods consumed in many Asian countries. Instant noodles have become internationally recognized food, and worldwide consumption is on the rise. The properties of instant noodles like taste, nutrition, convenience, safety, longer shelf-life, and reasonable price have made them popular. Quality factors important for instant noodles are color, flavor, and texture, cooking quality, rehydration rates during final preparation, and the presence or absence of rancid taste after extended storage. Microstructure of dough and noodles has been studied to understand the influence of ingredients and processing variables on the noodle quality by employing scanning electron microscopy. Applications of newer techniques like confocal laser scanning microscopy and epifluorescence light microscopy employed to understand the microstructure changes in dough and noodles have also been discussed. Sincere efforts of researchers are underway to improve the formulation, extend the shelf life, and promote universal fortification of instant noodles. Accordingly, many researchers are exploring the potential of noodle fortification as an effective public health intervention and improve its nutritional properties. This review focuses on the functionality of ingredients, unit operations involved, quality criteria for evaluation, recent trends in fortification, and current knowledge in relation to instant noodles.

http://www.ncbi.nlm.nih.gov/pubmed/24564594



Ramen Noodles in convenient single serving packages that include a chemical laden "flavor packet" are an indigestible food product. This food product passes through your body mostly undigested, leaving behind zero nutrients on a pathway littered with damage. The Ramen noodles on the left are indigestible and the home-made pasta noodles on the right are digesting as they should. These photos were taken with a pill camera and the left image was taken at 1 minute 44 seconds and the right image was taken at 1 minute 10 seconds.

South Korea: Ramen Noodle Capital of the World

Asians tend to eat more noodles than others, says the study. South Koreans in particular eat a heck of a lot of ramen noodles, as it turns out. They are per capita the population which eats more ramen noodles than any other country in the world — 3.4 billion packages in 2010 alone.

Unfortunately, in recent years South Korean health problems have steadily increased. The population is getting fatter and experiencing greater rates of heart disease than ever before. These facts led researchers to decide South Korea was the natural choice for a closer look at exactly what effect high instant noodle consumption has on the human body. The results weren't good at all.

"While instant noodle intake is greater in Asian communities, the association between instant noodle consumption and metabolic syndrome has not been widely studied," said Dr. Hyun Joon Shin, lead scientist for this study. "I decided to investigate in order to uncover more distinct connections."

Women Hit Harder By Poor Food Choices

Using information gleaned from a national health and nutrition survey conducted between 2007 and 2009, Dr. Shin and his colleagues reviewed data on over 10,000 South Korean adults aged 19 to 64. They discovered that people who ate instant noodles of any type — whether ramen, lo mein, Thai, or glass — more than twice a week tended to suffer from a condition called metabolic syndrome.

According to the National Institutes of Health:

Metabolic syndrome is the name for a group of risk factors that raises your risk for heart disease and other health problems, such as diabetes and stroke. The term "metabolic" refers to the biochemical processes involved in the body's normal functioning. Risk factors are traits, conditions, or habits that increase your chance of developing a disease.

South Korean women who ate the most processed ramen noodles were demonstrably more likely to suffer from metabolic syndrome, according to the study. Here's the kicker: This was true no matter what other foods they regularly ate or how much they exercised. Even those who lived on an unhealthy fast food diet but no instant noodles were less likely to have metabolic syndrome than those who ate ramen noodles at least twice a week on an otherwise healthy diet. That's just scary. Women appear to suffer more ill effects than men from high ramen consumption. Dr. Shin believes this is so, in part, because of differences in hormone levels and metabolism between men and women.

Ramen noodles are particularly unhealthy because they contain a food additive called Tertiary-butyl hydroquinone (TBHQ), a preservative that is a petroleum industry by-product. They're also incredibly high in sodium, calories and saturated fat.

The containers packaging these noodles aren't helping much either. The dreaded chemical bisphenol-A (BPA) is widely used in the styrofoam cups in which we often buy our ramen noodle lunches. Among other things, BPA may be a carcinogen. It is also considered a hormone disruptor, negatively affecting natural hormones in our bodies such as estrogen. Bisphenol A's seemingly weak estrogenic effect actually wreaks havoc in our bodies in ways we never expected. Between the preservatives and the packaging, instant noodles are a minefield of potential health problems. The more you eat, and the more regularly you eat them, the worse it is. It's just not worth the risk.

Yet Again, Proof That We Should Avoid Processed Foods

We shouldn't need more evidence, but this study provides it. Instant and processed foods are the worst possible meal choices we can make. Want visual proof that you really need to avoid processed ramen noodles? Watch this video, which shows what goes on in your stomach after you eat them. Ramen noodles and similar processed foods aren't digestible and travel through your body mostly whole, leaving no nutrients behind with the certain damage they cause along their travels through the bowels of your body.

Youtube:

https://www.youtube.com/watch?v=IQlNv2Au-Lg

Healthier options need not be that much more expensive than ramen noodles. Beans, vegetables, grains and even organic pasta and a host of other whole, natural foods can replace cheap instant noodles without affecting your wallet. Shop carefully and they'll provide an immune boosting nutritional burst without breaking your bank but more importantly, they won't endanger your health.

Journal Of The American College Of Nutrition • October 2011

Dairy products and cancer

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Abstract

"Cancer is a group of more than 100 diseases in which cells display uncontrolled growth, invasion, and sometimes metastasis. Milk and dairy products contain micronutrients and several bioactive constituents that may influence cancer risk and progression. Much of the focus of human, population-based studies has been on the effects of intake of milk and total dairy products or of calcium intake. Based on a systematic review of the epidemiologic literature, the World Cancer Research Fund and American Institute for Cancer Research report concluded there was a probable association between milk intake and lower risk of colorectal cancer, a probable association between diets high in calcium and increased risk of prostate cancer, and limited evidence of an association between milk intake and lower risk of bladder cancer. For other cancers, the evidence was mixed or lacking. Since the 2007 report, several additional, large-cohort studies have been published, including two that show an inverse association between intake of cultured dairy products and bladder cancer. Little is known about the potential effect of various bioactives produced during rumen microbe metabolism on cancer risk. Furthermore, studies support a role of live microbes present in some dairy products in the modulation of the human gut microbial community and gut metabolism. Given the growing appreciation for the role of the gut microbial community in relation to immune function and health and disease, including cancer, the potential role of various dairy products in the modulation of the human gut microbiome warrants further evaluation. Key teaching points: As a dietary exposure, dairy products are a complex group of foods and composition varies by region, which makes evaluation of their association with disease risk difficult. For most cancers, associations between cancer risk and intake of milk and dairy products have been examined only in a small number of cohort studies, and data are inconsistent or lacking. Meta-analyses of cohort data available to date support an inverse association between milk intake and risk of colorectal and bladder cancer and a positive association between diets high in calcium and risk of prostate cancer. Other constituents of dairy products, such as rumen-derived metabolites, have not been evaluated extensively for cancer-preventive properties. The influence of live microbes in fermented dairy products and certain cheeses on the human gut microbiome and immune function is a growing area of study."

http://www.ncbi.nlm.nih.gov/pubmed/22081693

Journal Of Lipid Research • August 2010

A Western-like fat diet is sufficient to induce a gradual enhancement in fat mass over generations

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Abstract

"The prevalence of obesity has steadily increased over the last few decades. During this time, populations of industrialized countries have been exposed to diets rich in fat with a high content of linoleic acid and a low content of alpha-linolenic acid compared with recommended intake. To assess the contribution of dietary fatty acids, male and female mice fed a high-fat diet (35% energy as fat, linoleic acid:alpha-linolenic acid ratio of 28) were mated randomly and maintained after breeding on the same diet for successive generations. Offspring showed, over four generations, a gradual enhancement in fat mass due to combined hyperplasia and hypertrophy with no change in food intake. Transgenerational alterations in adipokine levels were accompanied by hyperinsulinemia. Gene expression analyses of the stromal vascular fraction of adipose tissue, over generations, revealed discrete and steady changes in certain important players, such as CSF3 and Nocturnin. Thus, under conditions of genome stability and with no change in the regimen over four generations, we show that a Western-like fat diet induces a gradual fat mass enhancement, in accordance with the increasing prevalence of obesity observed in humans."

Full text, graphs, charts and 55 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903802/

“Prevalence of overweight was 34% in women and 50% in men; prevalence of obesity was 23% in both men and women.”

BMC • September 2008

Italian network for obesity and cardiovascular disease surveillance: A pilot project

Cinzia Lo Noce, Ovidio Brignoli, Gabriele Riccardi, Paola Ciccarelli, Francesco Dima, Luigi Palmieri and Simona Giampaoli

Abstract

Background

Also in Mediterranean countries, which are considered a low risk population for cardiovascular disease (CVD), the increase in body mass index (BMI) has become a public health priority. To evaluate the feasibility of a CVD and obesity surveillance network, forty General Practitioners (GPs) were engaged to perform a screening to assess obesity, cardiovascular risk, lifestyle habits and medication use.

Methods

A total of 1,046 women and 1,044 men aged 35–74 years were randomly selected from GPs' lists stratifying by age decade and gender. Anthropometric and blood pressure measurements were performed by GPs using standardized methodologies. BMI was computed and categorized in normal weight (BMI 18.5–24.9 kg/m2), overweight (BMI 25.0–29.9 kg/m2) and obese (BMI ≥ 30 kg/m2). Food frequency (per day: fruits and vegetables; per week: meat, cheese, fish, pulses, chocolate, fried food, sweet, wholemeal food, rotisserie food and sugar drink) and physical activity (at work and during leisure time) were investigated through a questionnaire. CVD risk was assessed using the Italian CUORE Project risk function.

Results

The percentage of missing values was very low. Prevalence of overweight was 34% in women and 50% in men; prevalence of obesity was 23% in both men and women. Level of physical activity was mostly low or very low. BMI was inversely associated with consumption of pulses, rotisserie food, chocolate, sweets and physical activity during leisure time and directly associated with consumption of meat. Mean value of total cardiovascular risk was 4% in women and 11% in men. One percent of women and 16% of men were at high cardiovascular risk (≥ 20% in 10 years). Normal weight persons were four times more likely to be at low risk than obese persons.

Conclusion

This study demonstrated the feasibility of a surveillance network of GPs in Italy focusing on obesity and other CVD risk factors. It also provided information on lifestyle habits, such as diet and physical activity.

Full Report with Graphs, Charts and 42 References

http://bmcfampract.biomedcentral.com/articles/10.1186/1471-2296-9-53

“A diet low in sodium, high in potassium, and rich in fruits, vegetables, whole grains, cereal fiber, and fatty fish **will likely reduce the incidence of stroke.**”

Neurology • February 2006

Optimal dietary habits for the prevention of stroke

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Abstract

Diet may influence stroke risk via several mechanisms, but the optimal dietary habits for stroke prevention are not well established. We reviewed English-language MEDLINE publications from January 1979 through November 2004 for experimental, observational, and clinical studies of dietary factors (minerals, fats, cholesterol, fish, animal protein, fiber, whole grains, carbohydrate quality, fruits and vegetables, antioxidants, B vitamins, dietary patterns) and risk of stroke or hypertension, the principal modifiable stroke risk factor. A total of 121 publications were selected based on relevance and quality of design and methods. Diets low in sodium and high in potassium lower blood pressure which will likely reduce stroke risk. Consumption of fruits and vegetables, whole grains, folate, and fatty fish are each likely to reduce stroke risk. A prudent or traditional Mediterranean dietary pattern, which incorporates these individual dietary components as well as intake of legumes and olive oil, may also prevent stroke. Evidence is limited or inconsistent regarding optimal levels of dietary magnesium, calcium, antioxidants, total fat, other fat subtypes, cholesterol, carbohydrate quality, or animal protein for stroke prevention. A diet low in sodium, high in potassium, and rich in fruits, vegetables, whole grains, cereal fiber, and fatty fish will likely reduce the incidence of stroke. Further research is needed regarding the possible effects of other major dietary factors on stroke risk.

http://www.ncbi.nlm.nih.gov/pubmed/16479440

The Medical Journal Of Australia • August 2006

Health benefits of herbs and spices: the past, the present, the future

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Abstract

Herbs and spices have a traditional history of use, with strong roles in cultural heritage, and in the appreciation of food and its links to health. Demonstrating the benefits of foods by scientific means remains a challenge, particularly when compared with standards applied for assessing pharmaceutical agents. Pharmaceuticals are small-molecular-weight compounds consumed in a purified and concentrated form. Food is eaten in combinations, in relatively large, unmeasured quantities under highly socialised conditions. The real challenge lies not in proving whether foods, such as herbs and spices, have health benefits, but in defining what these benefits are and developing the methods to expose them by scientific means.

CULTURAL ASPECTS

The place of herbs and spices in the diet needs to be considered in reviewing health benefits. This includes definitions of the food category and the way in which benefits might be viewed, and therefore researched. Research may focus on identifying bioactive substances in herbs and spices, or on their properties as a whole food, and/or be set in the context of a dietary cuisine.

THE ROLE OF HERBS AND SPICES IN HEALTH

The antioxidant properties of herbs and spices are of particular interest in view of the impact of oxidative modification of low-density lipoprotein cholesterol in the development of atherosclerosis. There is level III-3 evidence (National Health and Medical Research Council [NHMRC] levels of evidence) that consuming a half to one clove of garlic (or equivalent) daily may have a cholesterol-lowering effect of up to 9%. There is level III-1 evidence that 7.2 g of aged garlic extract has been associated with anticlotting (in-vivo studies), as well as modest reductions in blood pressure (an approximate 5.5% decrease in systolic blood pressure). A range of bioactive compounds in herbs and spices have been studied for anticarcinogenic properties in animals, but the challenge lies in integrating this knowledge to ascertain whether any effects can be observed in humans, and within defined cuisines. Research on the effects of herbs and spices on mental health should distinguish between cognitive decline associated with ageing and the acute effects of psychological and cognitive function. There is level I and II evidence for the effect of some herbal supplements on psychological and cognitive function. There is very limited scientific evidence for the effects of herbs and spices on type 2 diabetes mellitus, with the best evidence being available for the effect of ginseng on glycaemia, albeit based on four studies. More research is required, particularly examining the effects of chronic consumption patterns. With increasing interest in alternatives to non-steroidal anti-inflammatory agents in the management of chronic inflammation, research is emerging on the use of food extracts. There is level II evidence for the use of ginger in ameliorating arthritic knee pain; however, the improvement is modest and the efficacy of ginger treatment is ranked below that of ibuprofen. More definitive research is required.

PUBLIC HEALTH AND DIETARY IMPLICATIONS

Recommendations for intakes of food in the Australian guide to healthy eating do not yet include suggested intakes of herbs and spices. Future consideration should be given to including more explicit recommendations about their place in a healthy diet. In addition to delivering antioxidant and other properties, herbs and spices can be used in recipes to partially or wholly replace less desirable ingredients such as salt, sugar and added saturated fat in, for example, marinades and dressings, stir-fry dishes, casseroles, soups, curries and Mediterranean-style cooking. Vegetable dishes and vegetarian options may be more appetising when prepared with herbs and spices.

FUTURE DIRECTIONS

As several metabolic diseases and age-related degenerative disorders are closely associated with oxidative processes in the body, the use of herbs and spices as a source of antioxidants to combat oxidation warrants further attention. Immediate studies should focus on validating the antioxidant capacity of herbs and spices after harvest, as well as testing their effects on markers of oxidation. This will work in parallel with clinical trials that are aiming to establish antioxidants as mediators of disease prevention. From a dietary perspective, the functionality of herbs and spices will be exposed through consideration of their properties as foods. As with most foods, the real benefits of including them in the diet are likely to emerge with a better understanding of the attributes of health that are best supported by food, and in methodological developments addressing the evidence base for their effects. These developments are well underway through evidence-based frameworks for substantiating health claims related to foods. At present, recommendations are warranted to support the consumption of foods rich in bioactive components, such as herbs and spices. With time, we can expect to see a greater body of scientific evidence supporting the benefits of herbs and spices in the overall maintenance of health and protection from disease.

http://www.ncbi.nlm.nih.gov/pubmed/17022438

“The role of diet in cancer is a major public health issue.”

Journal Of The British Menopause Society • December 2006

Nutrition and cancer risk: an overview

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Abstract

The role of diet in cancer is a major public health issue. Foods associated with a low risk of cancer are those typically included in the so-called Mediterranean diet, which is also associated with low mortality rates from cardiovascular disease. Implementing such a diet would involve increasing the consumption of fruits, vegetables, cereals, whole-grain foods and fish, while reducing the intake of refined carbohydrates and red meat. In addition, olive oil should replace saturated fats. Omega-3 fatty acids found in fish inhibit the growth in vitro of colon, breast and prostate cancers. Fibre can bind bile acids, which produce carcinogenic metabolites, and fermented fibre produces volatile fatty acids that can protect against colon cancer. It has been hypothesized that the anti-cancer actions of olive oil may relate to the ability of its mono-unsaturated fatty acid, oleic acid, to regulate oncogenes.

http://www.ncbi.nlm.nih.gov/pubmed/17178013

“The number of lives potentially saved annually from the selected outcomes if fruit and vegetable intake increased to 600 g person per day reached 892,000 and 423,000 in the EU-15 and EU-10, respectively; total disease burden could decrease by 1.9% and 3.6%, respectively.**”**

Public Health Nutrition • August 2006

The burden of cardiovascular disease and cancer attributable to low fruit and vegetable intake in the European Union: differences between old and new Member States

Author information

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Abstract

OBJECTIVE

To estimate the burden of disease attributable to low fruit and vegetable intake in the 15 countries that were members of the European Union (EU) before May 2004 (EU-15) and the 10 countries that then joined it (EU-10).

DESIGN

Data on fruit and vegetable intake, target levels of intake and estimates of relative risks, deaths and disability were combined to obtain the burden of ischaemic heart disease, ischaemic stroke and four types of cancer (lung/bronchus/trachea, stomach, oesophagus, and colon/rectum) attributable to low fruit and vegetable consumption.

SETTING

EU-15 and EU-10 Member States.

RESULTS

The number of lives potentially saved annually from the selected outcomes if fruit and vegetable intake increased to 600 g person(-1) day(-1) reached 892,000 and 423,000 in the EU-15 and EU-10, respectively; total disease burden could decrease by 1.9% and 3.6%, respectively. The burden of ischaemic heart disease and stroke could be reduced by up to 17% and 10%, respectively, in the EU-15 and by 24% and 15%, respectively, in the EU-10; potential reductions for the selected cancers varied from 1% to 12% in the EU-15 and from 2% to 17% in the EU-10.

CONCLUSIONS

The potential health gain of increased fruit and vegetable intake is particularly large in the new Member States, and particularly high for cardiovascular diseases, a main cause of health divide in Europe. This stresses the need for better nutrition programmes and policies that take account of economic, social and cultural specificities.

http://www.ncbi.nlm.nih.gov/pubmed/16923289

“Dietary fats associated with an increased risk of Coronary Heart Disease include trans-fats and saturated fats ... Dietary sodium is associated with elevation of blood pressure ...”

Public Health Nutrition • February 2004

Diet, nutrition and the prevention of hypertension and cardiovascular diseases

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Abstract

Cardiovascular diseases (CVD) are growing contributors to global disease burdens, with epidemics of CVD advancing across many regions of the world which are experiencing a rapid health transition. Diet and nutrition have been extensively investigated as risk factors for major cardiovascular diseases like coronary heart disease (CHD) and stroke and are also linked to other cardiovascular risk factors like diabetes, high blood pressure and obesity. The interpretation of evidence needs to involve a critical appraisal of methodological issues related to measurement of exposures, nature of outcome variables, types of research design and careful separation of cause, consequence and confounding as the basis for observed associations. Adequate evidence is available, from studies conducted within and across populations, to link several nutrients, minerals, food groups and dietary patterns with an increased or decreased risk of CVD. Dietary fats associated with an increased risk of CHD include trans-fats and saturated fats, while polyunsaturated fats are known to be protective. Dietary sodium is associated with elevation of blood pressure, while dietary potassium lowers the risk of hypertension and stroke. Regular frequent intake of fruits and vegetables is protective against hypertension, CHD and stroke. Composite diets (such as DASH diets, Mediterranean diet, ‘prudent’ diet) have been demonstrated to reduce the risk of hypertension and CHD. Sufficient knowledge exists to recommend nutritional interventions, at both population and individual levels, to reduce cardiovascular risk. That knowledge should now be translated into policies which promote healthy diets and discourage unhealthy diets. This requires coordinated action at the level of governments, international organizations, civil society and responsible sections of the food industry.

http://www.ncbi.nlm.nih.gov/pubmed/14972059

“These findings should serve as a strong incentive for the initiation of intervention trials that will test the effect of specific dietary patterns in the prevention and management of patients with cancer.”

European Journal of Cancer Prevention • June 2004

The traditional diet of Greece and cancer

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Abstract

The term ‘Mediterranean diet’, implying that all Mediterranean people have the same diet, is a misnomer. The countries around the Mediterranean basin have different diets, religions and cultures. Their diets differ in the amount of total fat, olive oil, type of meat, wine, milk, cheese, fruits and vegetables; and the rates of coronary heart disease and cancer, with the lower death rates and longer life expectancy occurring in Greece. The diet of Crete represents the traditional diet of Greece prior to 1960. Analyses of the dietary pattern of the diet of Crete shows a number of protective substances, such as selenium, glutathione, a balanced ratio of n-6/n-3 essential fatty acids (EFA), high amounts of fibre, antioxidants (especially resveratrol from wine and polyphenols from olive oil), vitamins E and C, some of which have been shown to be associated with lower risk of cancer, including cancer of the breast. Epidemiological studies and animal experiments indicate that n-3 fatty acids exert protective effects against some common cancers, especially cancers of the breast, colon and prostate. Many mechanisms are involved, including suppression of neoplastic transformation, cell growth inhibition, and enhanced apoptosis and anti-angiogenicity, through the inhibition of eicosanoid production from n-6 fatty acids; and suppression of cyclooxygenase 2 (COX-2), interleukin 1 (IL-1) and IL-6 gene expression by n-3 fatty acids. Recent intervention studies in breast cancer patients indicate that n-3 fatty acids, and docosahexaenoic acid (DHA) in particular, increase the response to chemopreventive agents. In patients with colorectal cancer, eicosapentaenoic acid (EPA) and DHA decrease cell proliferation, and modulate favourably the balance between colonic cell proliferation and apoptosis. These findings should serve as a strong incentive for the initiation of intervention trials that will test the effect of specific dietary patterns in the prevention and management of patients with cancer.

http://www.ncbi.nlm.nih.gov/pubmed/15167223

“Broader adherence to recommendations for daily intake of fruit, vegetables, fish and fatty acid composition **may take away as much as 20-30% of the burden of cardiovascular disease** ...”

European Journal Of Cardiovascular Prevention And Rehabilitation • February 2010

Food and vessels: the importance of a healthy diet to prevent cardiovascular disease

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Abstract

AIM

We attempted to quantify the burden of cardiovascular disease that can be prevented by broader adherence to recommendations on dietary intake of key nutrients.

METHODS

A computer model capturing the epidemiology of chronic disease and risk factors in the Dutch population was used to simulate differences in the occurrence of cardiovascular disease under various scenarios defined by levels of intake of saturated and trans fatty acids, fruit, vegetables and fish. The following scenarios were compared with the current situation: (i) the whole population adhering to recommendations (optimum scenario); (ii) a moderate improvement and (iii) increased intake of fruit as has been achieved in an actual intervention (‘fruit at work’). Other outcome measures assessed were (differences in) life expectancy and healthy life expectancy for a 40-year-old individual.

RESULTS

In the optimum scenario, cumulative incidence prevented over a period of 20 years was 240,000 cases for acute myocardial infarction, or 30% of the expected number of cases, 328,000 (16%) for other coronary heart disease and 215,000 (21%) for stroke. For the moderate improvement scenario, the corresponding figures were 119,000 (14%), 163 000 (8%) and 105,000 (10%), respectively. The individual contributions of each of the separate dietary factors were greatest for fish, followed in decreasing order by fruit, vegetables, saturated and trans fatty acids. Only fish and fruit contributed to a decrease in strokes. In the optimum scenario, 1 year was added to the life expectancy of a 40-year-old individual and half a year in the moderate improvement scenario.

CONCLUSION

Broader adherence to recommendations for daily intake of fruit, vegetables, fish and fatty acid composition may take away as much as 20-30% of the burden of cardiovascular disease and result in approximately 1 extra life year for a 40-year-old individual. Promotion of a healthy diet should be given more emphasis in the prevention of cardiovascular disease.

http://www.ncbi.nlm.nih.gov/pubmed/19593150

“Empirical evidence suggests that a considerable fraction of all **cancer incidences** [19-32%] **can be prevented by a higher intake of fruit and vegetables.**”

Public Health And Nutrition • February 2003

Increased intake of fruit and vegetables: estimation of impact in terms of life expectancy and healthcare costs

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Abstract

OBJECTIVES

There is strong evidence that a high consumption of fruit and vegetables reduces the risk of developing many cancers. This study examined the economic consequences for the healthcare sector if people followed the recommendations and increased their intake of fruit and vegetables.

DESIGN

A life table was used to describe a base case population with respect to life expectancy, cancer incidence and healthcare costs. Relative risks of cancer for a high versus a low intake of fruit and vegetables were obtained from the literature and were used to simulate populations with a higher intake of fruit and vegetables. The empirical data consist of a 20% sample of the Danish population that was followed from 1993 to 1997. Civil registration numbers were used to link various computerised registers, in order to describe each individual in the sample in terms of morbidity, mortality and healthcare costs.

RESULTS

The average daily intake of fruit and vegetables was assumed to be approximately 250 g for the general Danish population. Simulated intakes of 400 g and 500 g increased the life expectancy by 0.8 and 1.3 years, respectively. In addition, it was estimated that 19% and 32% of the cancer incidence could be prevented. The aggregate healthcare costs remained stable, as the resources saved due to a lower cancer incidence were offset by healthcare costs imposed by the fact that healthy people live longer and require more healthcare. However, the variations across age groups and health sectors were substantial.

DISCUSSION

The study adopted a healthcare sector perspective. Only costs from hospitalisation and primary care were included in the calculations. The costs of changing people’s dietary habits, i.e. education, information and promotion as well as other costs that would be relevant from a societal perspective, have not been taken into account. Furthermore, the transition from one level of intake to another is not the focus of the analysis, although it might take decades to observe the full effect of the dietary changes.

CONCLUSION

Empirical evidence suggests that a considerable fraction of all cancer incidences can be prevented by a higher intake of fruit and vegetables. That may result in improved public health (gain in life years) at no additional cost to the healthcare sector.

http://www.ncbi.nlm.nih.gov/pubmed/12581462

“This review focuses on the role of dietary factors in the pathogenesis of **asthma and chronic obstructive pulmonary disease.**”

Current Allergy & Asthma Reports • March 2003

Dietary factors in the pathogenesis of asthma and chronic obstructive pulmonary disease

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Abstract

This review focuses on the role of dietary factors in the pathogenesis of asthma and chronic obstructive pulmonary disease. Reduced pulmonary function and indicators of airway obstruction have been shown to be strong indicators of mortality; therefore, a link with diet in the pathogenesis of these diseases would have important public health implications. The results of the studies identified in the review suggest that people who have a diet rich in fruit and vegetables have a lower risk of poor respiratory health, and that this may be due to the antioxidant nutrients these foods contain. On the basis of the evidence, it seems justified to promote a healthy diet, high in fruits, vegetables, and whole grain foods and low in alcohol and fatty foods, as set out in existing guidelines for prevention of cardiovascular disease and cancer, to protect respiratory health in both children and adults.

http://www.ncbi.nlm.nih.gov/pubmed/12562552

“Evidence from prospective cohort studies indicates that a **high consumption of plant-based foods such as fruit and vegetables, nuts, and whole grains is associated with a significantly lower risk of coronary artery disease and stroke.**”

American Journal Of Clinical Nutrition • September 2003

Plant-based foods and prevention of cardiovascular disease: an overview

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Abstract

Evidence from prospective cohort studies indicates that a high consumption of plant-based foods such as fruit and vegetables, nuts, and whole grains is associated with a significantly lower risk of coronary artery disease and stroke. The protective effects of these foods are probably mediated through multiple beneficial nutrients contained in these foods, including mono- and polyunsaturated fatty acids, n-3 fatty acids, antioxidant vitamins, minerals, phytochemicals, fiber, and plant protein. In dietary practice, healthy plant-based diets do not necessarily have to be low in fat. Instead, these diets should include unsaturated fats as the predominant form of dietary fat (eg, fats from natural liquid vegetable oils and nuts), whole grains as the main form of carbohydrate, an abundance of fruit and vegetables, and adequate n-3 fatty acids. Such diets, which also have many other health benefits, deserve more emphasis in dietary recommendations to prevent chronic diseases.

Full text, charts, graphs and 64 references:

http://www.ajcn.nutrition.org/content/78/3/544S.long

“Genetic and environmental factors, including diet and life-style, both contribute to cardiovascular disease, cancers, and other major causes of mortality, but various lines of evidence indicate that **environmental factors are most important.**”

Science • April 2002

Balancing life-style and genomics research for disease prevention

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Abstract

Genetic and environmental factors, including diet and life-style, both contribute to cardiovascular disease, cancers, and other major causes of mortality, but various lines of evidence indicate that environmental factors are most important. Overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health. However, integration of new genetic information into epidemiologic studies can help clarify causal relations between both life-style and genetic factors and risks of disease. Thus, a balanced approach should provide the best data to make informed choices about the most effective means to prevent disease.

http://www.ncbi.nlm.nih.gov/pubmed/11976443

Annals Of Internal Medicine • June 2001

The effect of fruit and vegetable intake on risk for coronary heart disease

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> “Consumption of fruits and vegetables, particularly green leafy vegetables and vitamin C-rich fruits and vegetables, **appears to have a protective effect against coronary heart disease.**”

Abstract

BACKGROUND
Many constituents of fruits and vegetables may reduce the risk for coronary heart disease,
but data on the relationship between fruit and vegetable consumption and risk for coronary heart disease are sparse.
OBJECTIVE
To evaluate the association of fruit and vegetable consumption with risk for coronary heart disease.
DESIGN
Prospective cohort study.
SETTING
The Nurses’ Health Study and the Health Professionals’ Follow-Up Study.
PARTICIPANTS
84 251 women 34 to 59 years of age who were followed for 14 years and 42 148 men 40 to 75 years who were followed for 8 years.
All were free of diagnosed cardiovascular disease, cancer, and diabetes at baseline.
MEASUREMENTS
The main outcome measure was incidence of nonfatal myocardial infarction or fatal coronary heart disease
(1127 cases in women and 1063 cases in men). Diet was assessed by using food-frequency questionnaires.
RESULTS
After adjustment for standard cardiovascular risk factors, persons in the highest quintile of fruit and vegetable intake had a relative risk for coronary heart disease of 0.80 (95% CI, 0.69 to 0.93) compared with those in the lowest quintile of intake. Each 1-serving/d increase in intake of fruits or vegetables was associated with a 4% lower risk for coronary heart disease (relative risk, 0.96 [CI, 0.94 to 0.99]; P = 0.01, test for trend). Green leafy vegetables (relative risk with 1-serving/d increase, 0.77 [CI, 0.64 to 0.93]), and vitamin C-rich fruits and vegetables (relative risk with 1-serving/d increase, 0.94 [CI, 0.88 to 0.99]) contributed most to the apparent protective effect of total fruit and vegetable intake.
CONCLUSIONS
Consumption of fruits and vegetables, particularly green leafy vegetables and vitamin C-rich fruits and vegetables,
appears to have a protective effect against coronary heart disease.

http://www.ncbi.nlm.nih.gov/pubmed/11412050

“Increasing the intake of vegetables and fruit is feasible and could result in considerable improvements in public health within the European Union.”

Public Health And Nutrition • August 2001

The potential contribution of increased vegetable and fruit consumption to health gain in the European Union

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Abstract

BACKGROUND

The risk of many important diseases can be reduced by consuming a diet rich in vegetables and fruit. For this reason the World Health Organization (WHO) recommends a daily intake of more than 400 g person(-1). The pattern of both the supply and intake of vegetables and fruit and the potential health gain achieved by increasing intake in the European Union (EU) and three accession countries are presented in this paper.

METHODS

Patterns of supply and dietary intake were assessed using (1) FAO food balance sheets, which allow comparison between the levels of supply in countries but do not reflect actual intake; and (2) survey data reflecting dietary intake. Using WHO mortality data for coronary heart and cerebrovascular disease and major cancers up to age 65 years, the number of preventable deaths is estimated, assuming vegetable and fruit consumption were levelled up to that of the highest consuming group, and assuming relative risks of 0.5, 0.7 or 0.9.

RESULTS

Vegetable and fruit consumption varies considerably between EU Member States. The populations of about half (seven) of the EU Member States have a mean daily intake of less than 275 g. Using the best current estimates of relative risk, over 26,000 deaths before the age of 65 years would be prevented annually in the EU if intake was levelled up to the highest consumption levels (and about double this number of deaths before the age of 75 years).

CONCLUSION

Increasing the intake of vegetables and fruit is feasible and could result in considerable improvements in public health within the EU. Priority should be given to developing methods that demonstrate the burden of disease caused by too low intakes of vegetables and fruit. This would enable the appropriate social, cultural and economic policies to be developed within the EU.

http://www.ncbi.nlm.nih.gov/pubmed/11527513

“Analyses of the dietary pattern of the diet of Crete shows a number of protective substances, such as selenium, glutathione, a balanced ratio of (n-6):(n-3) essential fatty acids (EFA), high amounts of fiber, antioxidants (especially resveratrol from wine and polyphenols from olive oil), vitamins E and C, **some of which have been shown to be associated with lower risk of cancer, including cancer of the breast.**”

American Institute for Cancer Research 11th Annual Research Conference on Diet, Nutrition and Cancer

The Journal Of Nutrition • November 2001

The Mediterranean diets: What is so special about the diet of Greece? The scientific evidence

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Abstract

The term “Mediterranean diet,” implying that all Mediterranean people have the same diet, is a misnomer. The countries around the Mediterranean basin have different diets, religions and cultures. Their diets differ in the amount of total fat, olive oil, type of meat and wine intake; milk vs. cheese; fruits and vegetables; and the rates of coronary heart disease and cancer, with the lower death rates and longer life expectancy occurring in Greece. Extensive studies on the traditional diet of Greece (the diet before 1960) indicate that the dietary pattern of Greeks consists of a high intake of fruits, vegetables (particularly wild plants), nuts and cereals mostly in the form of sourdough bread rather than pasta; more olive oil and olives; less milk but more cheese; more fish; less meat; and moderate amounts of wine, more so than other Mediterranean countries. Analyses of the dietary pattern of the diet of Crete shows a number of protective substances, such as selenium, glutathione, a balanced ratio of (n-6):(n-3) essential fatty acids (EFA), high amounts of fiber, antioxidants (especially resveratrol from wine and polyphenols from olive oil), vitamins E and C, some of which have been shown to be associated with lower risk of cancer, including cancer of the breast. These findings should serve as a strong incentive for the initiation of intervention trials that will test the effect of specific dietary patterns in the prevention and management of patients with cancer.

Full text, free PDF, charts, graphs and 114 references

http://jn.nutrition.org/content/131/11/3065S.full.pdf

Epidemiologic Reviews • December 2001

Diet and obstructive lung diseases

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Abstract

The results presented in this review suggest that the impact of nutrition on obstructive lung disease is most evident for antioxidant vitamins, particularly vitamin C and, to a lesser extent, vitamin E. By decreasing oxidant insults to the lung, antioxidants could modulate the development of chronic lung diseases and lung function decrement. Antioxidant vitamins could also play an important role in gene-environment interactions in complex lung diseases such as childhood asthma. Data also suggest that omega-3 fatty acids may have a potentially protective effect against airway hyperreactivity and lung function decrements; however, relevant data are still sparse. Although epidemiologic data suggest that consumption of fresh fruit may reduce risk of noncarcinogenic airway limitation, there are no clear data on which nutrients might be most relevant. While some studies evaluate daily intake of vitamin C, other studies use fruit consumption as a surrogate for antioxidant intake. Given the dietary intercorrelations among antioxidant vitamins, particularly vitamin C, beta-carotene, and flavonoids, as well as other micronutrients, it may be difficult to isolate a specific effect. Some population subgroups with higher levels of oxidative stress, such as cigarette smokers, may be more likely to benefit from dietary supplementation, since some studies have suggested that antioxidant intake may have a greater impact in this group. Studies of lung function decrement and COPD in adults suggest that daily intake of vitamin C at levels slightly exceeding the current Recommended Dietary Allowance (60 mg/day among nonsmokers and 100 mg/day among smokers) may have a protective effect (20). In the Schwartz and Weiss (85) and Britton et al. (87) studies, an increase of 40 mg/day in vitamin C intake led to an approximate 20-ml increase in FEV1. Daily mean vitamin C intakes in these studies were 66 mg and 99.2 mg, respectively, and the highest intake level (178 mg/day) was approximately three times the Recommended Dietary Allowance. Although the amplitude of the effect was modest, if these effects accumulate over 20-30 years, they could have a meaningful impact on the rate at which pulmonary function declines, particularly in symptomatic subjects (85). Longitudinal data support the hypothesis that fresh fruit consumption has a beneficial impact on the lung (95). Among children, consumption of fresh fruit, particularly fruit high in vitamin C, has been related to a lower prevalence of asthma symptoms and higher lung function (64). This effect was observed event at low levels of fruit consumption (one or two servings per week vs. less than one serving per week), which suggests that a small increase in dietary intake could have a beneficial effect. Consumption of fish has also been related to lower airway hyperreactivity among children (75) and higher lung function in adults (100); however, longitudinal data do not provide evidence that increased omega-3 fatty acid intake protects against lung disease (101). Experimental studies of persons with asthma suggest that magnesium infusion may have a place in the acute treatment of asthma, but it does not seem to have long-term benefits. The studies of sodium, selenium, and fish oils do not show convincing evidence of clinical benefits. Studies of vitamin C supplementation suggest a short-term protective effect on airway responsiveness and pulmonary function. It remains to be proven whether consistent use of vitamin C would have a protective effect on the evolution of chronic asthma. Results from supplementation studies conducted among subjects exposed to high levels of oxidants (57-60) suggest that daily intake of antioxidant vitamins exceeding the Recommended Dietary Allowance may have a beneficial effect on lung airways and that intake higher than the Recommended Dietary Allowance should be recommended for populations chronically exposed to photooxidant air pollutants (such as ozone), cigarette smoking, or vigorous exercise. It is difficult to determine the amounts of antioxidant vitamins that people should consume. In particular, although vitamin C was shown to have maximum bioavailability when given in a single dose of 200 mg (102), experiments on which this finding was based were conducted under normal conditions. Guidelines from the US National Cancer Institute (103) recommend consumption of five servings of fruit and vegetables daily, corresponding to a vitamin C intake exceeding 200 mg. Dietary surveys carried out in the US population indicate that less than 12 percent of US children and adults meet this recommended level of intake (104). Diet appears to be an important cofactor in the development of obstructive lung disease, although data are still sparse. There is a need for further research in experimental and epidemiologic settings to better understand the physiologic effects of antioxidant vitamins, omega-3 fatty acids, and other nutrients on lung tissues. The impact of diet on the incidence and evolution of asthma and COPD should be investigated using a cohort design that accounts for known risk factors. This will allow researchers to evaluate the exposure-disease relation over an adequate time frame and obtain insight into the causality of the relation. Some of these studies should enroll infants and young children to determine the impact of early diet on respiratory health. Research should also focus on the equally challenging policy issues--namely, finding effective methods of convincing people to increase their daily consumption of fresh fruits and vegetables, to stop smoking cigarettes, and to minimize their environmental and occupational exposure to pollutants and other agents that cause respiratory disease.

Full text, free PDF with charts, graphs and 104 references

http://epirev.oxfordjournals.org/content/23/2/268.full.pdf

“The lack of evidence of a general increase in energy intake among youths despite an increase in the prevalence of overweight suggests that physical inactivity is a major public health challenge in this age group.”

American Journal Of Clinical Nutrition • November 2000

Energy and fat intakes of children and adolescents in the united states: data from the national health and nutrition examination surveys

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Abstract

BACKGROUND

Dietary factors related to body weight and chronic disease risk are of interest because of recent increases in the prevalence of overweight.

OBJECTIVE

Secular trends in energy and fat intakes of youths aged 2-19 y were assessed. Current intakes were compared with recommendations.

DESIGN

Dietary 24-h recall data from the third National Health and Nutrition Examination Survey (1988-1994) and earlier national surveys were examined.

RESULTS

Mean energy intake changed little from the 1970s to 1988-1994 except for an increase among adolescent females. Over the same time period, the mean percentage of energy from total and saturated fat decreased, but remained above recommendations, with overall means of 33.5% of energy from fat and 12.2% of energy from saturated fat. In 1988-1994, approximately 1 in 4 youths met the recommendations for intakes of fat and saturated fat and 3 in 4 met the recommendation for cholesterol intake. Beverages contributed 20-24% of energy across all ages and soft drinks provided 8% of energy in adolescents. Except for adolescent girls, beverage energy contributions were generally higher among overweight than nonoverweight youths; soft drink energy contribution was higher among overweight youths than among nonoverweight youths for all groups.

CONCLUSIONS

The lack of evidence of a general increase in energy intake among youths despite an increase in the prevalence of overweight suggests that physical inactivity is a major public health challenge in this age group. Efforts to increase physical activity and decrease nonnutritive sources of energy may be important approaches to counter the rise in overweight prevalence.

http://www.ncbi.nlm.nih.gov/pubmed/11063476

“The epidemiological evidence for a relationship between diet and indicators of **asthma and chronic obstructive pulmonary disease (COPD) is evaluated.**”

Proceedings Of The Nutrition Society • May 1999

Dietary influences on chronic obstructive lung disease and asthma: a review of the epidemiological evidence

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Abstract

The epidemiological evidence for a relationship between diet and indicators of asthma and chronic obstructive pulmonary disease (COPD) is evaluated. The review focuses on the intake of Na, n-3 fatty acids, and antioxidant vitamins as well as fruit and vegetables. Experimental studies suggest that a high-Na diet has a small adverse effect on airway reactivity in asthma patients. However, observational studies provide no clear evidence that high Na intake has adverse effects on airway reactivity or asthma symptoms in open populations. n-3 Polyunsaturated fatty acids, which are present in fish oils, are metabolized into less broncho-constricting and inflammatory mediators than n-6 polyunsaturated fatty acids. Studies in the general adult population suggest that a high fish intake has a beneficial effect on lung function, but the relationship with respiratory symptoms and clinically-manifest asthma or COPD is less evident. Also, experimental studies in asthma patients have not demonstrated an improvement in asthma severity after supplementations with fish oil. Several studies showed a beneficial association between fruit and vegetable intake and lung function, but the relationship with respiratory symptoms and the clinically-manifest disease was less convincing. A similar pattern was found for vitamin C in relation to indicators of asthma and COPD, but there are still conflicting results with respect to vitamin E and beta-carotene. In conclusion, the epidemiological evidence for a beneficial effect on indicators of asthma and COPD of eating fish, fruit and vegetables is increasing. However, the effectiveness of dietary supplementation in open-population samples is often not demonstrated. Several unresolved questions are raised, which should be addressed in future studies on the relationship between diet and respiratory disease.

http://www.ncbi.nlm.nih.gov/pubmed/10466172

Cardiology Clinics • February 1996

Diet and heart disease: The role of fat, alcohol, and antioxidants

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Abstract

Overwhelming evidence indicates that the Western diet plays a major role in atherogenesis. Clinicians are only now beginning to tease out the precise components of the diet that are harmful or beneficial. With respect to fat intake, it remains unclear whether it is the amount or type of fat that promotes atherosclerotic disease. There appears to be a consistent positive association of cholesterol, saturated fat, and possibly trans-fatty acid intake and atherosclerotic disease. Although there is general agreement that reducing intake of these dietary components would be beneficial, controversy remains on what should replace these harmful fats. Some researchers advocate massive reductions in total fat consumption with replacement with carbohydrates for everyone, whereas others recommend a Mediterranean-style diet, which replaces saturated animal fats with vegetable fats. Very low-fat diets have been shown to lower the chance of a heart attack among those with severe coronary artery disease, but for the majority of Americans who do not have obvious artery disease, there is no convincing evidence that a very low-fat diet is optimal. There may be other adverse health effects of this Asian diet, such as increased rates of hemorrhagic stroke. Further research is required to refine thinking on the optimal composition of fats in diet. The effects of alcohol consumption on chronic diseases are complex. The strength and consistency of the observational and experimental evidence strongly suggests a causal link between light to moderate alcoholic beverage consumption and reduced risks of CHD. These reductions in risk of CHD appear to be mediated largely by raising HDL cholesterol levels, although additional mechanisms remain possible and do not appear to be beverage specific. Maximal benefit in terms of CHD appears to be at the level of one drink per day. From a public policy standpoint, whether the benefits for CHD persist at heavy drinking levels or are attenuated is moot because clear harm of heavy drinking in terms of overall mortality outweighs any benefits in the reduction of heart disease. Although the association of alcohol and CHD is likely to be causal, any individual or public health recommendations must consider the complexity of alcohol's metabolic, physiologic, and psychological effects. With alcohol, the differences between daily intake of small to moderate and large quantities may be the difference between preventing and causing disease. A discussion of alcohol intake should be a part of routine preventive counseling. Given the complex nature of alcohol disease relationships, alcohol consumption should not be viewed as a primary preventive strategy; also, it should not necessarily be viewed as an unhealthy behavior. Based on the totality of available evidence, antioxidants represent a possible but as yet unproven means to reduce risks of cardiovascular disease. Although it remains unclear whether supplementation of diet with antioxidant vitamins will reduce risks of atherosclerotic disease, most researchers agree that consumption of fruits and vegetables is an important part of a healthy diet. The U.S. Department of Agriculture recommends two to four servings of fruit and three to five servings of vegetables per day.

http://www.ncbi.nlm.nih.gov/pubmed/9072292

American Journal Of Clinical Nutrition • June 1995

Mediterranean diet and public health: personal reflections

Author information

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Abstract

“**My concern about diet as a public health problem began in the early 1950s in Naples, where we observed very low incidences of coronary heart disease associated with what we later came to call the “good Mediterranean diet.” The heart of this diet is mainly vegetarian, and differs from American and northern European diets in that it is much lower in meat and dairy products and uses fruit for dessert.** These observations led to our subsequent research in the Seven Countries Study, in which we demonstrated that saturated fat is the major dietary villain. Today, the healthy Mediterranean diet is changing and coronary heart disease is no longer confined to medical textbooks. Our challenge is to persuade children to tell their parents to eat as Mediterraneans do.”

http://www.ncbi.nlm.nih.gov/pubmed/7754982

“The number of lives potentially saved annually from the selected outcomes if fruit and vegetable intake increased to 600 g person(-1) day(-1) **reached 892,000**... The burden of ischaemic heart disease and stroke could be reduced by up to ... 24% and 15%, respectively [with] potential reductions for the selected cancers varied from 1% to 12% in the EU-15 and from 2% to 17% in the EU-10.**”**

The burden of cardiovascular disease and cancer attributable to low fruit and vegetable intake in the European Union: differences between old and new Member States

Public Health And Nutrition • August 2006

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Abstract

OBJECTIVE

To estimate the burden of disease attributable to low fruit and vegetable intake in the 15 countries that were members of the European Union (EU) before May 2004 (EU-15) and the 10 countries that then joined it (EU-10).

DESIGN

Data on fruit and vegetable intake, target levels of intake and estimates of relative risks, deaths and disability were combined to obtain the burden of ischaemic heart disease, ischaemic stroke and four types of cancer (lung/bronchus/trachea, stomach, oesophagus, and colon/rectum) attributable to low fruit and vegetable consumption.

SETTING

EU-15 and EU-10 Member States.

RESULTS

The number of lives potentially saved annually from the selected outcomes if fruit and vegetable intake increased to 600 g person(-1) day(-1) reached 892,000 and 423,000 in the EU-15 and EU-10, respectively; total disease burden could decrease by 1.9% and 3.6%, respectively. The burden of ischaemic heart disease and stroke could be reduced by up to 17% and 10%, respectively, in the EU-15 and by 24% and 15%, respectively, in the EU-10; potential reductions for the selected cancers varied from 1% to 12% in the EU-15 and from 2% to 17% in the EU-10.

CONCLUSIONS

The potential health gain of increased fruit and vegetable intake is particularly large in the new Member States, and particularly high for cardiovascular diseases, a main cause of health divide in Europe. This stresses the need for better nutrition programmes and policies that take account of economic, social and cultural specificities.

http://www.ncbi.nlm.nih.gov/pubmed/16923289

CHAPTER THREE

Bisphenol A • BPA, BPB, BPF, BPAF, BPS And TBBPA

BPA, short for the chemical bisphenol-A, which is commonly found in tin can linings and plastic, has been linked to different cancers, asthma, heart disease, and endocrine system dysfunction. Even though the Food and Drug Association deems it safe, it banned the use of BPA in baby bottles, sippy cups and infant formula packaging in 2012. The Industry responded to the ruling with a chemical that is not BPA, but close. It's called BPS or bisphenol-S and it's not any safer than the original. Just how scary is bisphenol-S?

According to a study published in the journal Environmental Health, products containing BPS may leach the type of estrogenic chemicals similar to BPA. Each week there seems to be a new study showing the havoc that bisphenol analogues wreak on our bodies.

• Exposure to BPA during pregnancy can cause oxidative damage that may put the baby at risk of developing diabetes or heart disease later in life, according to a January 2015 study published in Endocrinology.

• Washington State University researchers have found a direct link between BPA, and disrupted sperm production. Writing in the journal PLOS Genetics in January 2015, they say the chemical disrupts the delicate DNA interactions needed to create sperm.

The Peer Review

• Exposure to BPA may be linked to a dental abnormality in children called molar incisor hypomineralization (MIH), which affects approximately 18 percent of children ages 6 to 9, according to research presented at the Endocrine Society's 97th annual meeting in San Diego in March 2015. MIH causes white or brown opaque spots on an affected child's permanent first molars and incisors (the middle four teeth on the top and bottom), which become sensitive, painful and prone to cavities. This research might help answer what causes MIH. Until now, it was thought to have environmental origins, but from where was unclear.

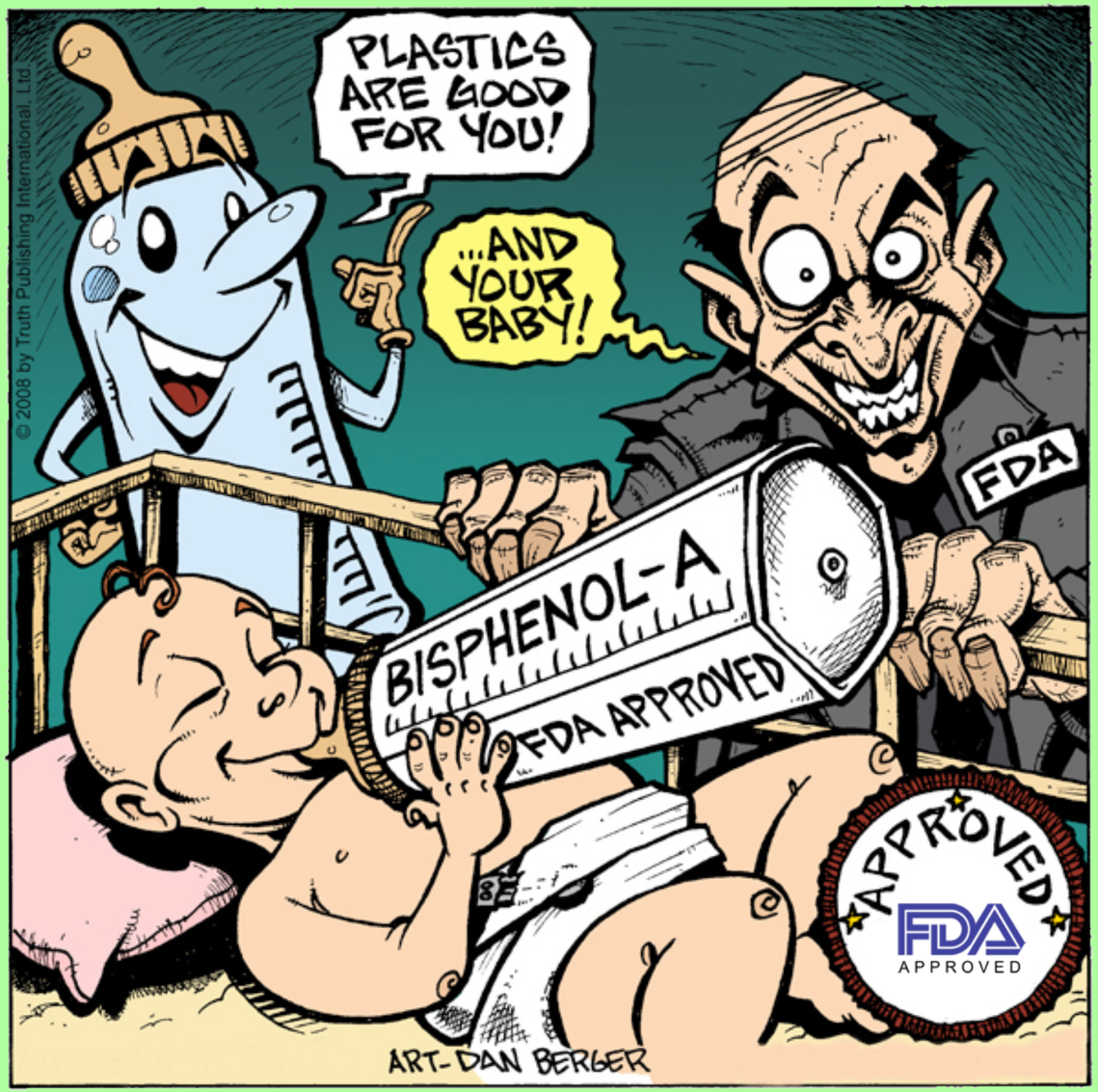
Considering this research was done by two government agencies—the FDA's National Center for Toxicological Research and the Department of Energy's Pacific Northwest National Laboratory—in conjunction with the American Chemical Society, it's a well-designed study that illustrates that there is a lot for us to learn about how this chemical is transferred to our bodies and its effects on our health.

So what should you do in the meantime? Stay away. Try to eliminate plastics from the kitchen, such as hard and soft plastic toys, straws, glasses and food containers. Reach for glass and stainless steel when available. Stay away from other items known to have bisphenol analogues, such as thermal paper, receipt paper, FedEx waybills, medical imaging results (e.g., ultrasounds), and deli meat paper although food products remain your primary source.

BPA is a dangerous human endocrine disruptor linked to a variety of disorders and diseases. Avoid canned foods, foods and beverages packaged in plastics, soups and juices in boxes or any product that might contain this human poison. Cash register receipts and newspapers are a contamination source of Bisphenol analogues. Don't handle them at all if you can help it. Because BPA and its analogues are in the air, water, soil and dust it's paramount that you become immediately proactive and eliminate all food sources of Bisphenol analogues from your life.

Bisphenol A and its analogues have been found in as much as 90% of populations tested, in blood, urine and breast milk, in various countries including the United States. That bisphenol analogues like BPF and BPS have quietly replaced BPA and companies marketing foods can make the claim that they aren't using BPA, contrasts sharply with reality and contradicts science.

PLASTIC FOOD ADDITIVES ARE POISONOUS TO THE HUMAN SPECIES



Toxicology • January 2016

Impairment of object recognition memory by maternal bisphenol A exposure is associated with inhibition of Akt and ERK/CREB/BDNF pathway in the male offspring hippocampus

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Abstract

Bisphenol A (BPA) is a commonly used endocrine-disrupting chemical used as a component of polycarbonates plastics that has potential adverse effects on human health. Exposure to BPA during development has been implicated in memory deficits, but the mechanism of action underlying the effect is not fully understood. In this study, we investigated the effect of maternal exposure to BPA on object recognition memory and the expressions of proteins important for memory, especially focusing on the ERK/CREB/BDNF pathway. Pregnant Sprague-Dawley female rats were orally treated with either vehicle or BPA (0.05, 0.5, 5 or 50mg/kgBW/day) during days 9-20 of gestation. Male offspring were tested on postnatal day 21 with the object recognition task. Recognition memory was assessed using the object recognition index (index=the time spent exploring the novel object/(the time spent exploring the novel object+the time spent exploring the familiar object)). In the test session performed 90min after the training session, BPA-exposed male offspring not only spent more time in exploring the familiar object at the highest dose than the control, but also displayed a significantly decreased the object recognition index at the doses of 0.5, 5 and 50mg/kgBW/day. During the test session performed 24h after the training session, BPA-treated males did not change the time spent exploring the familiar object, but had a decreased object recognition index at 5 and 50mg/kgBW/day, when compared to control group. These findings indicate that object recognition memory was susceptible to maternal BPA exposure. Western blot analysis of hippocampi from BPA-treated male offspring revealed a decrease in Akt, phospho-Akt, p44/42 MAPK and phospho-p44/42 MAPK protein levels, compared to controls. In addition, BPA significantly inhibited the levels of phosphorylation of CREB and BDNF in the hippocampus. Our results show that maternal BPA exposure may full impair object recognition memory, and that impairment may be related to a decrease in Akt activation and an inhibition of the ERK/CREB/BDNF pathway in the hippocampus. This study also adds new evidence that suggests BPA has an antagonistic effect on the action of estrogen in the brain.

http://www.ncbi.nlm.nih.gov/pubmed/26827910

“Exposure to BPA during development has been implicated in **memory deficits** ... These findings indicate that object recognition memory was susceptible to maternal BPA exposure. Our results show that maternal BPA exposure may **fully impair object recognition memory** ... This study also adds new evidence that suggests **BPA has an antagonistic effect on the action of estrogen in the brain.**”

“BPA causes a disturbance in ß-catenin signaling via a superoxide anion overload.”

Environmental Toxicology • January 2016

BPA-toxicity via superoxide anion overload and a deficit in ß-catenin signaling in human bone mesenchymal stem cells

Author information

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Abstract

Bisphenol A (BPA), used in the manufacture of products based on polycarbonate plastics and epoxy resins, is well known as an endocrine-disrupting monomer. In the current study, BPA increased cytotoxicity in hBMSCs in a dose- and time-dependent manner, concomitantly with increased lipid peroxidation. Increased cell death in BPA-treated cells was markedly blocked by pretreatment with the superoxide dismutase mimetic MnTBAP and MnTMPyP, but not by catalase, glutathione, the glutathione peroxidase mimetic ebselen, the NOS inhibitor NAME, or the xanthine oxidase inhibitor allopurinol. Furthermore, the decline in nuclear ß-catenin and cyclin D1 levels in hBMSCs exposed to BPA was reversed by MnTBAP treatment. Finally, treatment of hBMSCs with the GSK3ß inhibitor LiCl2 increased nuclear ß-catenin levels and significantly attenuated cytotoxicity compared with BPA treatment. Our current results in hBMSCs exposed to BPA suggest that BPA causes a disturbance in ß-catenin signaling via a superoxide anion overload.

http://www.ncbi.nlm.nih.gov/pubmed/26822619

“**Exposure to bisphenol A** (BPA), an endocrine disrupting chemical, **during gestation is associated with a variety of metabolic dysfunctions in adulthood, including hyperinsulinemia, glucose intolerance and insulin resistance.** This study provides novel insight into the effects of BPA exposure on the fetal pancreata, indicating alterations in glucagon expression in islets and islet cell clusters.”

Hormone Molecular Biology And Clinical Investigation • January 2016

Prenatal exposure to bisphenol A alters mouse fetal pancreatic morphology and islet composition

By Whitehead R, Guan H, Arany E, Cernea M, Yang K.

Abstract

BACKGROUND

Exposure to bisphenol A (BPA), an endocrine disrupting chemical, during gestation is associated with a variety of metabolic dysfunctions in adulthood, including hyperinsulinemia, glucose intolerance and insulin resistance. These modifications in glucose homeostasis largely stem from alterations in pancreatic function. However, the effects of BPA on the fetal pancreas have never been explored. The present study addressed this important question by examining the effects of prenatal BPA exposure on the mouse fetal pancreatic development.

MATERIALS AND METHODS

Pregnant mice were fed a BPA diet (25 mg BPA/kg diet) from embryonic day 7.5 (E7.5) to E18.5. At E18.5, fetal pancreata were collected and analyzed for morphological changes in the endocrine pancreas such as islet size, number and beta and alpha cell distribution.

RESULTS

We showed that BPA exposed fetal pancreata had a greater number of islet-cell clusters (ICCs; <300 µm2; $p<0.05$) compared with controls. Furthermore, immunohistochemical analysis revealed that prenatal BPA exposure increased both glucagon expression in islets and the numbers of glucagon-expressing islet-cell clusters ($p<0.05$).

CONCLUSION

Considering that ICCs represent the initial stages of islet development in the fetal pancreas, our findings suggest that BPA promotes islet differentiation or delays the conversion of ICCs into mature islets. Moreover, the increase in glucagon expression suggests a potential alteration in the alpha: beta-cell ratio in islets, which may have significant implications for the fetal pancreas both structurally and functionally. This study provides novel insight into the effects of BPA exposure on the fetal pancreata, indicating alterations in glucagon expression in islets and ICCs.

http://www.ncbi.nlm.nih.gov/pubmed/26812801

Environmental Pollution • January 2016

Ecotoxicity of bisphenol A to Caenorhabditis elegans by multigenerational exposure and variations of stress response in vivo across generations

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Abstract

In order to understand how bisphenol A (BPA) exposure acts on the evolutionary dynamics of populations and changes of stress response across generations, the model animal Caenorhabditis elegans was used to conduct the multigenerational testing. Multiple endpoints at the physiological (growth, reproduction, and locomotion behaviors) and molecular (stress-related gene expressions) levels were examined by multigenerational exposure to low-concentration BPA (0.001-10 μM) across four generations. The results showed that changes of physiological-level effects across four generations varied in magnitude and direction, depending on the exposure concentrations. C. elegans individuals in the first generation grew smaller, moved slower, and produced less offsprings than the controls by BPA exposure. As for each trait tested, the first generation response could be commonly mirrored in the subsequent generations at the highest concentration of 10 μM. However, at lower concentrations, response of parental generation was a relatively poor predictor of the effects on progeny, as acclimation or cumulative damage could occur in the subsequent generations. The integrated gene expression profiles visually illustrated that the tested gene expressions at low concentrations (0.001-0.01 μM) were more obviously changed in both G1 and G4 generations, and the G1 generation showed a much greater degree of increase in stress-related gene expressions than the G4 generation. The multigenerational toxicity data emphasize the need of considering biological effects over multiple generations to conduct accurate assessment of environmental risks of toxicants on population dynamics.

http://www.ncbi.nlm.nih.gov/pubmed/26561446

“In order to understand how bisphenol A (BPA) exposure acts on the evolutionary dynamics of populations and changes of stress response across generations, the model animal Caenorhabditis elegans was used to conduct the multigenerational testing.

The multigenerational toxicity data emphasize the need of considering biological effects over multiple generations to conduct accurate assessment of environmental risks of toxicants on population dynamics.”

Reproductive Toxicology • January 2016

Use of a rat ex-vivo testis culture method to assess toxicity of select known male reproductive toxicants

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Abstract

Due to the complex physiology of the testes, in vitro models have been largely unsuccessful at modeling testicular toxicity in vivo. We conducted a pilot study to evaluate the utility of the Durand ex vivo rat seminiferous tubule culture model [1-3] that supports spermatogenesis through meiosis II, including the formation of round spermatids. We used this system to evaluate the toxicity of four known testicular toxicants: 1,3-dinitrobenzene (DNB), 2-methoxyacetic acid (MAA), bisphenol A (BPA), and lindane over 21 days of culture. This organotypic culture system demonstrated the ability to successfully model in vivo testicular toxicity (Sertoli cell toxicity and disruption of meiosis) for all four compounds. These findings support the application of this system to study molecules and evaluate mechanisms of testicular toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/26802500

“**We used this system to evaluate the toxicity of four known testicular toxicants**: 1,3-dinitrobenzene (DNB), 2-methoxyacetic acid (MAA), **bisphenol A (BPA)**, and lindane over 21 days of culture. This organotypic culture system demonstrated the ability to successfully model in vivo testicular toxicity (Sertoli cell toxicity and disruption of meiosis) for all four compounds. **These findings support the application of this system to study molecules and evaluate mechanisms of testicular toxicity.**”

Toxicology Mechanisms And Methods • February 2016

Exposure to bisphenol A (BPA) in Wistar rats reduces sperm quality with disruption of ERK signal pathway

Author information

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Abstract

Bisphenol A (BPA) is an estrogenic environmental toxin widely used in the production of plastics and ubiquitous human exposure to this chemical has been proposed to be a potential risk to human health. Exposure to BPA can negatively impact sperm quality. However, the mechanism remains largely unknown. The objectives of this study were to assess the role of BPA on sperm quality and explore the possible mechanisms. The Wistar male rats (aged 28 days) were administered BPA by oral gavage for 28 days at dose of 50, 100 and 200 mg/kg/day; meanwhile, the negative control with corn oil (0 mg/kg/day BPA) and positive control with E2 at the dose of 100 µg/kg/day. The sperm density, sperm activity and sperm survival rate were analyzed byCASA system, and the sperm abnormality rate was analyzed by improved Papanicolaou stained. The protein expression levels of Src/p-Src, ERK1/2, p-ERK1/2 and CREB/p-CREB were detected by Western bolt. The results showed that the body weight gain, testes weight, testis coefficient, sperm density, sperm activity, sperm survival rate and protein expression levels of p-ERK1, p-ERK2 and p-CREB decreased, but the sperm abnormality rate increased with increasing BPA concentrations. There were positive correlations between sperm density, sperm activity and sperm survival rate with protein expression levels of p-ERK1, p-ERK2 and p-CREB, and negative correlations between sperm abnormality rate with the protein expression levels of p-ERK1, p-ERK2 and p-CREB. Results from the structural equation model demonstrated that BPA retained a significant negative effect to p-ERK, whereas p-ERK retained a significant positive effect to sperm quality and acted as the mediate variable. This study provides a novel insight regarding the potential role of p-ERK1 and p-ERK2 protein kinase on reproductive toxicity of BPA. The adverse effects of BPA on adult male sperm quality may be through the induction of the disruption of ERK signal pathway. However, additional research is needed to confirm our findings and to further test the suggested potential mechanisms.

http://www.ncbi.nlm.nih.gov/pubmed/26862991

“**Exposure to BPA can negatively impact sperm quality. However, the mechanism remains largely unknown.** The results showed that the body weight gain, testes weight, testis coefficient, sperm density, sperm activity, sperm survival rate and protein expression levels of p-ERK1, p-ERK2 and p-CREB decreased, but **the sperm abnormality rate increased with increasing BPA concentrations.** The adverse effects of BPA on adult male sperm quality may be through the induction of the disruption of ERK signal pathway.”

“These results showed that bisphenol AF and thiodiphenol (TDP) exerted cell biological effect, estrogenic, and thyroidal effect potentials **greater than those of BPA**. The cytotoxicity and endocrine disrupting effects of other BPs are **similar to or slightly lower than those of BPA.** Therefore, as potential alternatives to BPA, endocrine disrupting effects and potential health harm **of alternative Bisphenols to human[s] can also not be ignored.**”

Environmental Toxicology • February 2016

In vitro profiling of toxicity and endocrine disrupting effects of bisphenol analogues by employing MCF-7 cells and two-hybrid yeast bioassay

Author information

Amway

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Abstract

The potentially adverse health implications of bisphenol A (BPA) have led to increasing use of alternative bisphenols (BPs). However, little is known about the toxicity of alternative BPs. In this study, the cytotoxicity, genotoxicity, intracellular ROS formation, and Ca2+ fluctuation effects of BPs on MCF-7 cells were evaluated. At the same time, the estrogenic and thyroidal hormone effect potentials of six BPs were also evaluated using two-hybrid yeast bioassay. The results showed that most BPs at 0.01-1 μM significantly increased cell viability in MCF-7 cells and at higher exposure concentrations of 25-100 μM, they caused a significant decrease of cell viability. At the same time, these BPs also at 25-100 μM significantly increased LDH release of MCF-7 cells. In addition, several BPs at 10-50 μM resulted in a significantly concentration-depended increase in DNA-damaging effect on MCF-7 cells and elevated ROS production. Most BPs at 0.0001-10 μM significantly increased intracellular Ca2+ level. These results showed that bisphenol AF (BPAF) and thiodiphenol (TDP) exerted cell biological effect, estrogenic, and thyroidal effect potentials greater than those of BPA. The cytotoxicity and endocrine disrupting effects of other BPs are similar to or slightly lower than those of BPA. Therefore, as potential alternatives to BPA, endocrine disrupting effects and potential health harm of alternative BPs to human can also not be ignored.

http://www.ncbi.nlm.nih.gov/pubmed/26916392

FEBS Letters • February 2016

The Bisphenol A analogue Bisphenol S binds to K-Ras4B—implications for 'BPA-free' plastics

Author information

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Abstract

"K-Ras4B is a small GTPase that belongs to the Ras superfamily of guanine nucleotide-binding proteins. GTPases function as molecular switches in cells and are key players in intracellular signalling. Ras has been identified as an oncogene and is mutated in more than 20% of human cancers. Here, we report that Bisphenol S binds into a binding pocket of K-Ras4B previously identified for various low molecular weight compounds. **Our results advocate for more comprehensive safety studies on the toxicity of Bisphenol S, as it is frequently used for Bisphenol A-free food containers.**"

http://www.ncbi.nlm.nih.gov/pubmed/26867649

“**In total, 41 proteins were significantly altered by BPA exposure** compared to water or fructose controls. In conclusion, BPA exposure in the rats induces **major alterations in the myocardial proteome.**”

Toxicology • February 2016

Altered heart proteome in fructose-fed Fisher 344 rats exposed to bisphenol A

Abstract

Bisphenol A (BPA), is an artificial estrogen initially produced for medical purposes but is today widely used in polycarbonate plastics and epoxy resins. Exposure-related reproductive disorders have been found, but recently it has also been suggested that BPA may be involved in obesity, diabetes, myocardial hypertrophy and myocardial infarction in humans. To mimic a modern lifestyle, female rats were fed with fructose or fructose plus BPA (0.25mg/L drinking water). The myocardial left ventricle proteome of water controls, fructose-fed and fructose-fed plus BPA supplemented rats was explored. The proteome was investigated using nano-liquid chromatography tandem mass spectrometry and two-dimensional gel electrophoresis followed by matrix assisted laser desorption/ionization mass spectrometry identification. In total, 41 proteins were significantly altered by BPA exposure compared to water or fructose controls. Principal component analysis and cellular process enrichment analysis of altered proteins suggested increased fatty acid transport and oxidation, increased ROS generation and altered structural integrity of the myocardial left ventricle in the fructose-fed BPA-exposed rats, indicating unfavorable effects on the myocardium. In conclusion, BPA exposure in the rats induces major alterations in the myocardial proteome.

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http://www.ncbi.nlm.nih.gov/pubmed/26930160

Chemosphere • March 2016

Effects of bisphenol analogues on steroidogenic gene expression and hormone synthesis in H295R cells

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Abstract

The use of Bisphenol A (BPA) has been regulated in many countries because of its potential adverse effects on human health. As a result of the restriction, structural anologues such as bisphenol S (BPS) and bisphenol F (BPF) have already been used for industrial applications as alternatives to BPA. Bisphenol AF (BPAF) is mainly used as a crosslinker in the synthesis of specialty fluoroelastomers. These compounds have been detected in various environmental matrices and human samples. Previous studies have shown that these compounds have potential endocrine disrupting effects on wildlife and mammals in general. However, the effects on adrenocortical function and the underlying mechanisms are not fully understood. In the present study, the H295R cell line was used as a model to compare the cell toxicity and to investigate the potential endocrine disrupting action of four BPs (including BPA, BPS, BPF, and BPAF). The half lethal concentration (LC50) values at 72 h exposure indicated that the rank order of toxicities of the chemicals was BPAF > BPA > BPS > BPF. The hormone results demonstrated that BPA analogues, such as BPF, BPS and BPAF were capable of altering steroidogenesis in H295R cells. BPA and BPS exhibited inhibition of hormone production, BPF predominantly led to increased progesterone and 17ß-estradiol levels and BPAF showed induction of progesterone and reduction of testosterone. Inhibition effects of BPA and BPAF on hormone production were probably mediated by down-regulation of steroidogenic genes in H295R cells. However, the mechanisms of the endocrine interrupting action of BPF and BPS are still unclear, which may have additional mechanisms that have not been detected with BPA.

http://www.ncbi.nlm.nih.gov/pubmed/26751127

“The use of Bisphenol A (BPA) has been regulated in many countries because of its potential adverse effects on human health. As a result of the restriction, structural anologues such as bisphenol S (BPS) and bisphenol F (BPF) have already been used for industrial applications as alternatives to BPA. Previous studies have shown that these compounds have potential endocrine disrupting effects on wildlife and mammals in general. **BPA and BPS exhibited inhibition of hormone production, BPF predominantly led to increased progesterone and 17ß-estradiol levels and BPAF showed induction of progesterone and reduction of testosterone.**”

“Bisphenol A (BPA) is an estrogenic environmental toxin widely used in the production of plastics and ubiquitous **human exposure to this chemical has been proposed to be a potential risk to human health**. **Exposure to BPA can negatively impact sperm quality.**”

Toxicology Mechanisms And Methods • March 2016

Exposure to bisphenol A (BPA) in Wistar rats reduces sperm quality with disruption of ERK signal pathway

Author information

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Abstract

Bisphenol A (BPA) is an estrogenic environmental toxin widely used in the production of plastics and ubiquitous human exposure to this chemical has been proposed to be a potential risk to human health. Exposure to BPA can negatively impact sperm quality. However, the mechanism remains largely unknown. The objectives of this study were to assess the role of BPA on sperm quality and explore the possible mechanisms. The Wistar male rats (aged 28 days) were administered BPA by oral gavage for 28 days at dose of 50, 100 and 200 mg/kg/day; meanwhile, the negative control with corn oil (0 mg/kg/day BPA) and positive control with E2 at the dose of 100 µg/kg/day. The sperm density, sperm activity and sperm survival rate were analyzed byCASA system, and the sperm abnormality rate was analyzed by improved Papanicolaou stained. The protein expression levels of Src/p-Src, ERK1/2, p-ERK1/2 and CREB/p-CREB were detected by Western bolt. The results showed that the body weight gain, testes weight, testis coefficient, sperm density, sperm activity, sperm survival rate and protein expression levels of p-ERK1, p-ERK2 and p-CREB decreased, but the sperm abnormality rate increased with increasing BPA concentrations. There were positive correlations between sperm density, sperm activity and sperm survival rate with protein expression levels of p-ERK1, p-ERK2 and p-CREB, and negative correlations between sperm abnormality rate with the protein expression levels of p-ERK1, p-ERK2 and p-CREB. Results from the structural equation model demonstrated that BPA retained a significant negative effect to p-ERK, whereas p-ERK retained a significant positive effect to sperm quality and acted as the mediate variable. This study provides a novel insight regarding the potential role of p-ERK1 and p-ERK2 protein kinase on reproductive toxicity of BPA. The adverse effects of BPA on adult male sperm quality may be through the induction of the disruption of ERK signal pathway. However, additional research is needed to confirm our findings and to further test the suggested potential mechanisms.

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“Testicular steroidogenesis was altered by all bisphenol analogues tested.”

Toxicology • March 2016

Structural bisphenol analogues differentially target steroidogenesis in murine MA-10 Leydig cells as well as the glucocorticoid receptor

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Abstract

Although much information on the endocrine activity of bisphenol A (BPA) is available, a proper human hazard assessment of analogues that are believed to have a less harmful toxicity profile is lacking. Here the possible effects of BPA, bisphenol F (BPF), bisphenol S (BPS), as well as the brominated structural analogue and widely used flame retardant tetrabromobisphenol A (TBBPA) on human glucocorticoid and androgen receptor (GR and AR) activation were assessed. BPA, BPF, and TBBPA showed clear GR and AR antagonism with IC50 values of 67 µM, 60 µM, and 22 nM for GR, and 39 µM, 20 µM, and 982 nM for AR, respectively, whereas BPS did not affect receptor activity. In addition, murine MA-10 Leydig cells exposed to the bisphenol analogues were assessed for changes in secreted steroid hormone levels. Testicular steroidogenesis was altered by all bisphenol analogues tested. TBBPA effects were more directed towards the male end products and induced testosterone synthesis, while BPF and BPS predominantly increased the levels of progestagens that are formed in the beginning of the steroidogenic pathway. The MA-10 Leydig cell assay shows added value over the widely used H295R steroidogenesis assay because of its fetal-like characteristics and specificity for the physiologically more relevant testicular Δ4 steroidogenic pathway. Therefore, adding an in vitro assay covering fetal testicular steroidogenesis, such as the MA-10 cell line, to the panel of tests used to screen potential endocrine disruptors, is highly recommendable.

http://www.ncbi.nlm.nih.gov/pubmed/25576683

“Thus, these data supported the hypothesis that BPA exposure, during critical stages of adipose tissue development, may cause adipocyte metabolic dysfunction and inflammation, thereby **increasing the risk of developing obesity-related diseases.**”

PLoS One • March 2016

Low-Dose Bisphenol-A Impairs Adipogenesis and Generates Dysfunctional 3T3-L1 Adipocytes

Author information

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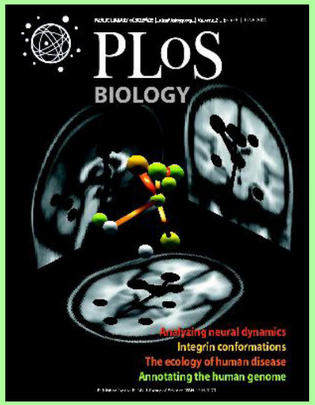
Abstract

Environmental endocrine disruptors (EDCs), including bisphenol-A (BPA), have been recently involved in obesity and diabetes by dysregulating adipose tissue function. Our aim was to examine whether prolonged exposure to low doses of BPA could affect adipogenesis and adipocyte metabolic functions. Therefore, 3T3-L1 pre-adipocytes were cultured for three weeks with BPA 1nM to mimic human environmental exposure. We evaluated BPA effect on cell proliferation, differentiation, gene expression and adipocyte metabolic function. BPA significantly increased pre-adipocyte proliferation ($p<0.01$). In 3T3-L1 adipocytes differentiated in the presence of BPA, the expression of Peroxisome proliferator-activated receptor gamma (PPARy), Fatty Acid Binding Protein 4/Adipocyte Protein 2 (FABP4/AP2) and CCAAT/enhancer binding protein (C/EBPa) was increased by 3.5, 1.5 and 3 folds, respectively. Mature adipocytes also showed a significant increase in lipid accumulation ($p<0.05$) and alterations of insulin action, with significant reduction in insulin-stimulated glucose utilization ($p<0.001$). Moreover, in mature adipocytes, mRNA levels of Leptin, interleukin-6 (IL6) and interferon-y (IFNy) were significantly increased ($p<0.05$). In conclusion, BPA prolonged exposure at low doses, consistent with those found in the environment, may affect adipocyte differentiation program, enhancing pre-adipocyte proliferation and anticipating the expression of the master genes involved in lipid/glucose metabolism. The resulting adipocytes are hypertrophic, with impaired insulin signaling, reduced glucose utilization and increased pro-inflammatory cytokine expression. Thus, these data supported the hypothesis that BPA exposure, during critical stages of adipose tissue development, may cause adipocyte metabolic dysfunction and inflammation, thereby increasing the risk of developing obesity-related diseases.



Full text, PDF, graphs, charts and 53 references

http://journals.plos.org/plosone/article/authors?id=10.1371%2Fjournal.pone.0150762

“In conclusion, **both in vivo administration and in vitro application of BPA impair mature sperm functions** by a CatSper-relevant mechanism.”

Toxicological Sciences • April 2016

Bisphenol A Impairs Mature Sperm Functions by a CatSper-Relevant Mechanism

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Abstract

Bisphenol A (BPA), an endocrine-disrupting chemical, is widely used in the manufacture of daily necessities. Previous studies showed that BPA could impair spermatogenesis. However, its effects on mature spermatozoa are not well known. We aimed to investigate the in vivo and in vitro toxicity of BPA on mature mouse spermatozoa. Different doses of BPA (0, 10, 50, and 250 μg·kg-1·d-1) were administrated orally to C57BL/6 mice for 8 weeks. Subsequently, the sperm viability, motility, acrosome reaction (AR) ratio together with the expression/current levels of the sperm-specific Ca2+ channel (CatSper) and K+ channel (KSper) were examined. These parameters were also evaluated after applying BPA directly to normal mouse sperm to appraise the toxicity of BPA to mature sperm in vitro Significant decreases in sperm motility and AR were found in BPA administrated mice, possibly resulting from a BPA caused CatSper down-regulation which was supported by both western blot and patch clamping results. Moreover, direct application of BPA to spermatozoa inhibited CatSper transiently and also caused significant reductions in sperm total motility and AR ratio. In conclusion, both in vivo administration and in vitro application of BPA impair mature sperm functions by a CatSper-relevant mechanism.

http://www.ncbi.nlm.nih.gov/pubmed/27125968

“These findings provide evidence of the mechanisms of action of BPA in a model vertebrate and **advocate for its reduction in the environment.**”

Epigenetics • April 2016

Bisphenol A causes reproductive toxicity, decreases dnmt1 transcription, and reduces global DNA methylation in breeding zebrafish (Danio rerio): An in silico approach

Author information

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Abstract

Bisphenol A (BPA) is a commercially important high production chemical widely used in epoxy resins and polycarbonate plastics, and is ubiquitous in the environment. Previous studies demonstrated that BPA activates estrogenic signaling pathways associated with adverse effects on reproduction in vertebrates and that exposure can induce epigenetic changes. We aimed to investigate the reproductive effects of BPA in a fish model and to document its mechanisms of toxicity. We exposed breeding groups of zebrafish (Danio rerio) to 0.01, 0.1, and 1 mg/L BPA for 15 d. We observed a significant increase in egg production, together with a reduced rate of fertilization in fish exposed to 1 mg/L BPA, associated with significant alterations in the transcription of genes involved in reproductive function and epigenetic processes in both liver and gonad tissue at concentrations representing hotspots of environmental contamination (0.1 mg/L) and above. Of note, we observed reduced expression of DNA methyltransferase 1 (dnmt1) at environmentally relevant concentrations of BPA, along with a significant reduction in global DNA methylation, in testes and ovaries following exposure to 1 mg/L BPA. Our findings demonstrate that BPA disrupts reproductive processes in zebrafish, likely via estrogenic mechanisms, and that environmentally relevant concentrations of BPA are associated with altered transcription of key enzymes involved in DNA methylation maintenance. These findings provide evidence of the mechanisms of action of BPA in a model vertebrate and advocate for its reduction in the environment.

http://www.ncbi.nlm.nih.gov/pubmed/27120497

“Low-dose and combined exposure to BPA and DES may have toxic effects on male fertility in the adult population.**”**

Environmental Toxicology And Pharmacology • April 2016

Low-dose and combined effects of oral exposure to bisphenol A and diethylstilbestrol on the male reproductive system in adult Sprague-Dawley rats

Author information

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Abstract

Study of the joint action of xenobiotics is important to fully explore their toxicity and complete risk analysis. In this study, we investigated the effects of low-dose and combined exposure of bisphenol A (BPA) and diethylstilbestrol (DES) on the reproductive system in adult male rats. The results showed that the sperm motility decreased in the BPA/DES and combined groups. Sperm deformity ratios and histological lesions of the testes were significantly higher and more significant, respectively, in the combined group compared with the single treated groups. No dose-effect relationship or significant additive effect on serum hormone levels was observed after combined exposure to BPA/DES. Ultrastructural results showed lesions of the Sertoli and Leydig cells, mainly in the endoplasmic reticulum (ER), in all treated groups. ER stress molecular sensor IRE1 was phosphorylated and activated after BPA and DES treatment in this study. The protein levels of ES stress molecular marker CHOP were significantly up-regulated after exposure to BPA, DES, and BPA and DES combined. These findings indicate that ER stress is important in BPA/DES-induced damage in rat testes. Low-dose and combined exposure to BPA and DES may have toxic effects on male fertility in the adult population.

http://www.ncbi.nlm.nih.gov/pubmed/26970683

“We hypothesize that **these chemicals could potentially impair the egg yolk formation** and eventually impact the zebra fish population which occupies an important niche among testing models used in drug discovery and related toxicity studies.”

Fish Physiology And Biochemistry • May 2016

Endocrine disruption by Bisphenol A, polychlorinated biphenyls and polybrominated diphenyl ether, in zebra fish (Danio rerio) model: an in silico approach

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Abstract

Endocrine disrupting chemicals may induce adverse health effects in humans and wildlife. Recent studies demonstrate that endocrine disrupting chemicals like Bisphenol A (BPA), polychlorinated biphenyls (PCBs) and polybrominated diphenyl ether (PBDE) affect the reproductive characters shared by wide range of creatures including fish. An attempt was made to evaluate the toxicity of these chemicals on the vitellogenin protein of zebra fish (Danio rerio) using in silico approach. The protein structure of zebra fish vitellogenin was predicted using homology modelling, and the stereochemical quality of the model was validated by Ramachandran plot. The 3-D structure of vitellogenin was docked with the aforementioned chemicals that have demonstrated endocrine-disrupting activity. The pair-wise alignments between vitellogenin with phosvitin, lipovitellin-2 and YGP40 obtained by CLUSTALW alignment suggest that the vitellogenin contained lipovitellin-2- phosvitin- and YGP40-related amino acid sequences. Based on the prediction of CASTp and CLUSTALW, BPA and PCB predominantly interacted with lipovitellin-2 site of the protein, while PBDE interacts predominantly with the YGP40 site of the vitellogenin protein. The results indicate that the endocrine-disrupting chemicals (BPA, PCB and PBDE) dock with the vitellogenin cleavage sites lipovitellin-2 and YGP40 that play a crucial role in lipid-protein complex formation in the egg yolk. We hypothesize that these chemicals could potentially impair the egg yolk formation and eventually impact the zebra fish population which occupies an important niche among testing models used in drug discovery and related toxicity studies.

http://www.ncbi.nlm.nih.gov/pubmed/27241054

“In the near future, higher concentrations of BPF and BPAF in surface waters are anticipated and for this reason further testing using test systems with various aquatic species and **endpoints are needed to provide additional information about toxic impacts of BPF and BPAF** on aquatic biota.**”**

Environmental Pollution • May 2016

Hazard identification and risk characterization of bisphenols A, F and AF to aquatic organisms

Author information

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Abstract

Production of bisphenol A (BPA) analogues such as bisphenol F (BPF) and bisphenol AF (BPAF) has recently increased, due to clear evidence of adverse effects of BPA on humans and wildlife. Bisphenols (BPs) have already been released into aquatic environment without previous available information about potential adverse effects of BPs and their potential risk to aquatic ecosystems. In this study, lethal and sublethal effects of BPF and BPAF to bacteria, algae, crustacea and fish embryos were investigated and the results were compared to the adverse effects obtained for BPA. We found that BPAF was the most toxic compound to Daphnia magna, Danio rerio and Desmodesmus subspicatus; the lowest 72 h EC50 (median effective concentration) and 21 d NOEC (no observed effect concentration) values were determined at 2.2 mg/L regarding zebrafish hatching success and 0.23 mg/L of BPAF obtained for growth and reproduction of water fleas, respectively. In most cases, BPA was more toxic to D. magna, D. rerio and D. subspicatus in comparison to BPF, but pigmentation of zebrafish embryos after 48 h of exposure and reproduction of water fleas after 21-day D. magna reproductive test exposure to BPF were much more impaired. Risk quotients (measured environmental concentration/21 d NOEC) showed that BPA, BPF and BPAF are recently not chronically hazardous to the survival, reproduction and growth of water fleas in surface waters. On the other hand, we importantly show that currently present BPAF concentrations in surface waters could cause a potential ecological risk to aquatic organisms. In the near future, higher concentrations of BPF and BPAF in surface waters are anticipated and for this reason further testing using test systems with various aquatic species and endpoints are needed to provide additional information about toxic impacts of BPF and BPAF on aquatic biota.

http://www.ncbi.nlm.nih.gov/pubmed/26957022

“The activation temperature appears to be the single most important parameter, i.e. a temperature increase from 40°C [104°F] to 70°C [158°F]results in an 80-fold rate increase [of persulfate oxidation]. Liquid chromatography time-of-flight mass spectrometry (LC-TOF-MS) **revealed the formation of eleven Transformation By-Products of BPA** ...**”**

Journal Of Environmental Management • May 2016

Oxidation of bisphenol A in water by heat-activated persulfate

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Abstract

The heat-activated persulfate oxidation of bisphenol A (BPA), a representative endocrine disrupting compound, was investigated with respect to the effect of several process variables on degradation rates. The activation temperature appears to be the single most important parameter, i.e. a temperature increase from 40 to 70 °C results in an 80-fold rate increase. Regarding initial BPA concentration, the reaction follows a pseudo-first order rate expression, where the kinetic constant decreases from 11.5 10-2 to 3.5 10-2 min-1 when BPA concentration increases from 110 to 440 μg/L. Reactions in actual water matrices, such as bottled water and secondary treated wastewater, are slower than in pure water since various organic/inorganic water constituents compete with BPA for being oxidized by the reactive oxidizing species; this was confirmed with experiments in pure water spiked with humic acid or bicarbonate. Interestingly though, the presence of chloride seems to promote BPA degradation. Furthermore, degradation is favored at near-neutral pH and increased sodium persulfate (SPS) concentrations. Experiments at an increased BPA concentration of 20 mg/L were performed to identify transformation by-products (TBPs), as well as assess the mineralization and toxicity of the treated samples. Liquid chromatography time-of-flight mass spectrometry (LC-TOF-MS) revealed the formation of eleven TBPs of BPA and plausible pathways including hydroxylation, oxidation, cleavage and oligomerization reactions are proposed. Mineralization occurs slower than BPA degradation, while the toxicity to marine bacteria Vibrio fischeri increases during the early stages of the reaction but it progressively decreases thereafter.

http://www.ncbi.nlm.nih.gov/pubmed/27240715

“... our study has considerable potential to predict late-onset chemical toxicities, **including abnormalities that occur during embryonic development.**”

Nucleic Acids Research • Oxford Journal • May 2016

Prediction of developmental chemical toxicity based on gene networks of human embryonic stem cells

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Abstract

Predictive toxicology using stem cells or their derived tissues has gained increasing importance in biomedical and pharmaceutical research. Here, we show that toxicity category prediction by support vector machines (SVMs), which uses qRT-PCR data from 20 categorized chemicals based on a human embryonic stem cell (hESC) system, is improved by the adoption of gene networks, in which network edge weights are added as feature vectors when noisy qRT-PCR data fail to make accurate predictions. The accuracies of our system were 97.5-100% for three toxicity categories: neurotoxins (NTs), genotoxic carcinogens (GCs) and non-genotoxic carcinogens (NGCs). For two uncategorized chemicals, **bisphenol-A** and permethrin, our system yielded reasonable results: bisphenol-A was categorized as an NGC, and permethrin was categorized as an NT; both predictions were supported by recently published papers. Our study has two important features: (i) as the first study to employ gene networks without using conventional quantitative structure-activity relationships (QSARs) as input data for SVMs to analyze toxicogenomics data in an hESC validation system, it uses additional information of gene-to-gene interactions to significantly increase prediction accuracies for noisy gene expression data; and (ii) using only undifferentiated hESCs, our study has considerable potential to predict late-onset chemical toxicities, including abnormalities that occur during embryonic development.

Full text, graphs, charts and 57 references

http://nar.oxfordjournals.org/content/early/2016/05/20/nar.gkw450.long

“The most important sublethal effects in embryos were cell dissociation and delayed development, whereas **the main abnormalities observed in larvae were related to neurotoxicity**, as scare response to stimuli and narcotic effect.**”**

Environmental Toxicology And Chemistry • May 2016

Developmental toxicity of bisphenol A diglycidyl ether (epoxide resin badge) during the early life cycle of a native amphibian species

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Abstract

Bisphenol A, diglycidyl ether (BADGE) is used in packaging materials, epoxy adhesives, additive for plastics but is also a potential industrial wastewater contaminant. The aim of this study was to evaluate the adverse effects of BADGE on Rhinella arenarum, by means of standardized bioassays at embryo-larval development. The results showed that BADGE was more toxic to embryos than to larvae at all exposure times. At acute exposure, lethality rates of embryos exposed to concentrations from 0.0005 mg/L BADGE were significantly higher than vehicle control, whereas lethality rates of larvae were significantly higher from 10 mg/L BADGE. Then, the toxicity increased significantly, with a LC50-96 h of 0.13 and 6.9 mg/L BADGE for embryos and larvae respectively. By the end of the chronic period the LC50-336 h were 0.04 and 2.2 mg/L BADGE for embryos and larvae respectively. This differential sensitivity was also ascertained by the 24-h pulse exposure experiments, in which embryos showed a stage-dependent toxicity, being blastula the most sensitive stage and S.23 the most resistant one. The most important sublethal effects in embryos were cell dissociation and delayed development, whereas the main abnormalities observed in larvae were related to neurotoxicity, as scare response to stimuli and narcotic effect.

http://www.ncbi.nlm.nih.gov/pubmed/27176149

“These preliminary results indicate noteworthy and **far-reaching effects of BPA on the reproductive system of male offspring**.”

Environmental Toxicology • June 2016

Prenatal bisphenol a exposure leads to reproductive hazards on male offspring via the Akt/mTOR and mitochondrial apoptosis pathways

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Abstract

BACKGROUND

Bisphenol A (BPA) exposure is ubiquitous, and in laboratory animals and humans, exposure has been associated with male spermatogenesis dysfunction. However, it is largely unknown if this association has a fetal origin.

OBJECTIVE

The aim of this research is to explore the mechanism whereby prenatal BPA exposure exerts its reproductive toxicities on spermatogenesis in male offspring.

METHODS

We fed pregnant SD rats BPA at doses ranging from 1 to 100 mg/kg body weight during gestation days 14-21. The male offspring were euthanized at postnatal day 21, and the levels of sex hormones and reactive oxygen species (ROS), expressions of proteins and genes in the Akt/mTOR, and mitochondrial apoptosis pathways were detected. Several closely linked autophagy indexes were also measured incidentally. Additionally, semen quality of adult offspring was tested at the end of the study.

RESULTS

The results revealed that prenatal BPA exposure can cause endocrine disruption and oxidative stress in male offspring, leading to inhibition of spermatogenesis by suppressing the Akt/mTOR pathway and activating the mitochondrial apoptosis pathway.

CONCLUSIONS

These preliminary results indicate noteworthy and far-reaching effects of BPA on the reproductive system of male offspring.

http://www.ncbi.nlm.nih.gov/pubmed/27296223

“The findings provide a framework for better understanding of **developmental toxicity of environmental contaminants in zebrafish and other vertebrate species.**”

Aquatic Toxicology • June 2016

Adverse morphological development in embryonic zebrafish exposed to environmental concentrations of contaminants individually and in mixture

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Abstract

Exposure to environmental contaminants has been linked to developmental and reproductive abnormalities leading to infertility, spontaneous abortion, reduced number of offspring, and metabolic disorders. In addition, there is evidence linking environmental contaminants and endocrine disruption to abnormal developmental rate, defects in heart and eye morphology, and alterations in behavior. Notably, these effects could not be explained by interaction with a single hormone receptor. Here, using a whole-organism approach, we investigated morphological changes to developing zebrafish caused by exposure to a number of environmental contaminants, including bisphenol A (BPA), di(2-ethylhexyl)phthalate (DEHP), nonylphenol, and fucosterol at concentrations measured in a local water body (Oldman River, AB), individually and in mixture. Exposure to nanomolar contaminant concentrations resulted in abnormal morphological development, including changes to body length, pericardia (heart), and the head. We also characterize the spatiotemporal expression profiles of estrogen, androgen, and thyroid hormone receptors to demonstrate that localization of these receptors might be mediating contaminant effects on development. Finally, we examined the effects of contaminants singly and in mixture. Combined, our results support the hypothesis that adverse effects of contaminants are not mediated by single hormone receptor signaling, and adversity of contaminants in mixture could not be predicted by simple additive effect of contaminants. The findings provide a framework for better understanding of developmental toxicity of environmental contaminants in zebrafish and other vertebrate species.

http://www.ncbi.nlm.nih.gov/pubmed/27107150

“Our findings first elaborate the mechanism of IGF-1-mediated BPA effects on neuronal differentiation, which is helpful to illuminate the **unique mechanism of BPA toxicity on prenatal neurodevelopment.**”

Molecular Neurobiology • June 2016

Bisphenol A Represses Dopaminergic Neuron Differentiation from Human Embryonic Stem Cells through Downregulating the Expression of Insulin-like Growth Factor 1

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Abstract

Bisphenol A (BPA) is a ubiquitous compound emerging as a possible toxicant during embryonic development. Human embryonic stem cell (hESC) promises a valuable model for evaluating the effects of environmental chemicals on human prenatal development. In our study, 1 μM BPA were applied to hESC-derived embryoid bodies (hEBs) and effects of BPA on neural cell differentiation were investigated. The expression level of insulin-like growth factor 1 (IGF-1) and marker genes for ectoderm, neuron progenitor cells, and dopaminergic (DA) neurons were all repressed upon BPA exposure. The population of hESC-derived neural precursor cells (NPCs) and DA neurons were decreased. Furthermore, yield of DA neuron-secreted tyrosine hydroxylase (TH) and dopamine were also reduced. When recombinant IGF-1 supplied, BPA-caused repressions were partially or completely relieved. Our further methylation microarray analysis indicated that there was a higher methylation level on the promoter of SRY-related HMG-box 5 (SOX5), a possible enhancer of IGF-1. Consistently, next quantitative polymerase chain reaction (qPCR) results confirmed that SOX5 expression was downregulated. Our investigation suggests that BPA represses DA neuron differentiation mainly through downregulating IGF-1 expression, which may attribute to the altered methylation level on the promoter of IGF-1 upstream genes. Our findings first elaborate the mechanism of IGF-1-mediated BPA effects on neuronal differentiation, which is helpful to illuminate the unique mechanism of BPA toxicity on prenatal neurodevelopment.

http://www.ncbi.nlm.nih.gov/pubmed/27271280

Environmental Science & Technology • June 2016

Bisphenol Analogues Other Than BPA: Environmental Occurrence, Human Exposure, and Toxicity-A Review

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Abstract

“Numerous studies have investigated the environmental occurrence, human exposure, and toxicity of bisphenol A (BPA). Following stringent regulations on the production and usage of BPA, several bisphenol analogues have been produced as a replacement for BPA in various applications. The present review outlines the current state of knowledge on the occurrence of bisphenol analogues (other than BPA) in the environment, consumer products and foodstuffs, human exposure and biomonitoring, and toxicity. Whereas BPA was still the major bisphenol analogue found in most environmental monitoring studies, BPF and BPS were also frequently detected. **Elevated concentrations of BPAF, BPF, and BPS (i.e., similar to or greater than that of BPA) have been reported in the abiotic environment and human urine from some regions. Many analogues exhibit endocrine disrupting effects, cytotoxicity, genotoxicity, reproductive toxicity, dioxin-like effects, and neurotoxicity in laboratory studies. BPAF, BPB, BPF, and BPS have been shown to exhibit estrogenic and/or antiandrogenic activities similar to or even greater than that of BPA**. Knowledge gaps and research needs have been identified, which include the elucidation of environmental occurrences, persistence, and fate of bisphenol analogues (other than BPA), sources and pathways for human exposure, effects on reproductive systems and the mammary gland, mechanisms of toxicity from coexposure to multiple analogues, metabolic pathways and products, and the impact of metabolic modification on toxicity.”

http://www.ncbi.nlm.nih.gov/pubmed/27143250

“Hence, **it appears that BPA affects the germ cells leading to impairment in the spermatogenesis**, and thus having its property as reproductive toxicant **and it also suppresses bone marrow functioning**, which leads to normocytic hypochromic anemia in rats.”

Veterinary World • June 2016

Evaluation of subacute bisphenol - A toxicity on male reproductive system

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Abstract

AIM

The aim was to evaluate the effect of multiple oral administration of bisphenol A (BPA) for 28 days on seminal characteristic on mammal using Wistar rat as a model.

MATERIALS AND METHODS

Rats were randomly divided into five different groups having 6 male rats in each group. The doses chosen were 50, 200, and 600 mg/kg body weight for Groups III, IV and V, respectively, based on preliminary dose range finding study and Group II served as vehicle control and Group I was negative control.

RESULTS

Reproductive study in the BPA-treated rats on day 28 revealed that there was significant ($p \leq 0.05$) reduction in the epididymal sperm count of rats of Group IV and significant ($p \leq 0.01$) decrease in Group V. Sperm motility percentage, dead count percentage, head and tail abnormality percentage were found to be significantly ($p \leq 0.01$) increased in rats of BPA-treated groups as compared to rats of control groups. Testes showed necrosis of germinal layer and spermatogonial cells in the seminiferous tubules. Hematological examination revealed significant ($p \leq 0.01$) decrease in the mean values of total erythrocyte count (TEC), total leukocyte count (TLC), hemoglobin, packed cell volume, and there was also significant ($p \leq 0.05$) lymphocytopenia in treated animals.

CONCLUSION

It can be concluded from this study that subacute toxicity of BPA caused a reduction in the epididymal sperm count, sperm motility, dead count, head and tail abnormality, as well as hematological indices such as TLC, TEC etc. Hence, it appears that BPA affects the germ cells leading to impairment in the spermatogenesis, and thus having its property as reproductive toxicant and it also suppresses bone marrow functioning, which leads to normocytic hypochromic anemia in rats.

Full text, photographic images, graphs, charts and 46 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4825275/

“The oligodendrocyte loss may thus represent an alternative route through which **early BPA exposure has its adversity on the brain and contributes to the development of neuropsychiatric illness.**”

Molecular Neurobiology • June 2016

Loss of Hippocampal Oligodendrocytes Contributes to the Deficit of Contextual Fear Learning in Adult Rats Experiencing Early Bisphenol A Exposure

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Abstract

During early development, continuous exposure to environmental contaminants such as bisphenol A (BPA) is known to alter neuronal development, resulting in aberrant brain structure and predisposing individuals to developing neuropsychiatric disorders later in life. While the altered oligodendrocyte (OL) structure and function have been casually linked to the occurrence of numerous psychiatric diseases, it remains open whether early BPA exposure (EBE) also recruits OLs to mediate its toxicity in the brain. Here, we observed that EBE from birth to postnatal day 21 caused a substantial loss of hippocampal OLs in rat pups. The OL loss was enduring and manifested even when the affected pups spanned into their adulthood. In parallel, the expression of two key proteins in mature OLs, myelin basic protein (MBP), and monocarboxylate transporter 1 (MCT1) was markedly downregulated in adult hippocampus with a considerable reduction in the number of myelinated axons. By contrast, the myelination of individual axons remained intact. The altered hippocampal OLs were related to EBE-mediated disruption of estrogen receptor (ER) signaling in developing OLs and could be readily prevented by treatment with low level of ICI 182780, an ER antagonist. Importantly, the adult rats subject to EBE exhibited clear deficit in contextual fear memory, which highly correlated with OL loss and decreased MBP and MCT1 expression in hippocampus. The OL loss may thus represent an alternative route through which EBE has its adversity on the brain and contributes to the development of neuropsychiatric illness.

http://www.ncbi.nlm.nih.gov/pubmed/27364615

“In conclusion, the lipophilicity of BPA and phthalates influence their toxicity to aquatic species.”

Bulletin Of Environmental Contamination And Toxicology • July 2016

Influence of Lipophilicity on the Toxicity of Bisphenol A and Phthalates to Aquatic Organisms

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Abstract

Bisphenol A (BPA) and phthalates are among the most popular plasticizers used today and have been reported ubiquitously in surface water, ground water, and sediment. For aquatic organisms, BPA was the most toxic (96 h LC50s) to aquatic invertebrates (0.96-2.70 mg/L) and less toxic to fish (6.8-17.9 mg/L). The toxicity of BPA to amphibians differed among developmental stages, with embryos having an LC50 of 4.6-6.8 mg/L and juveniles 0.50-1.4 mg/L. The toxicity of phthalates is affected by aromatic ring substitution, alkyl chain length, and metabolism. The toxicity (96 h LC50s) of phthalates was similar to aquatic invertebrates (0.46-377 mg/L) and fish (0.48-121 mg/L). In general, the toxicity of phthalates appears to be highest around a log KOW of 6, which corresponds to the highest potential for bioconcentration and bioaccumulation. In conclusion, the lipophilicity of BPA and phthalates influence their toxicity to aquatic species.

http://www.ncbi.nlm.nih.gov/pubmed/27169527

“Compared to the previous short-term toxicity evaluation, long-term exposure to BPA induced a more obvious response at the same concentration, and the phenomenon might be **due to cumulative toxic effects.”**

Chemosphere • July 2016

The chronic toxicity of bisphenol A to Caenorhabditis elegans after long-term exposure at environmentally relevant concentrations

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Abstract

To investigate biological effects of bisphenol A (BPA) over the long term, the model animal Caenorhabditis elegans was used to conduct the chronic exposure. C. elegans were exposed to BPA (0.0001-10 μM) from L4 larvae to day-10 adult in the present chronic toxicity assay system. Multiple endpoints at the physiological (growth, locomotion behaviors and lifespan), biochemical (lipofuscin accumulation), molecular (stress-related genes expressions), and population (population size) levels were examined. At the physiological level, BPA exposure induced significant negative effects on the indicators. Among the endpoints, head thrash was most sensitive and the detection limit was 0.001 μM. At the biochemical level, BPA exposure induced no significant effects on lipofuscin accumulation. At the molecular level, BPA induced strong stress responses in vivo. At the population level, the population size was significantly decreased in the treatment groups from 0.1 to 10 μM. Compared to the previous short-term toxicity evaluation, long-term exposure to BPA induced a more obvious response at the same concentration, and the phenomenon might be due to cumulative toxic effects. By the Pearson correlation analyses, cep-1 was speculated to act as an important role in BPA-induced chronic toxicity on C. elegans.

http://www.ncbi.nlm.nih.gov/pubmed/27085314

“The present study suggested that **BPA might cause the global DNA demethylation in gonads** of zebrafish by regulating the transcriptional changes of the DNA methylation/demethylation-associated genes (dnmts, gnmt, and tets).”

Ecotoxicology And Environmental Safety • August 2016

Global DNA methylation in gonads of adult zebrafish Danio rerio under bisphenol A exposure

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Abstract

Altered DNA methylation is pervasively associated with changes in gene expression and signal transduction after exposure to a wide range of endocrine disrupting chemicals. As a weak estrogenic chemical, bisphenol A (BPA) has been extensively studied for reproductive toxicity. In order to explore the effects of BPA on epigenetic modification in gonads of zebrafish Danio rerio, we measured the global DNA methylation together with the gene expression of DNA methyltransferase (dnmts), glycine N-methyltransferase (gnmt), and ten-eleven translocation (tets) in gonads of D. rerio under BPA exposure by ELISA and quantitative real-time PCR method, respectively. The global level of DNA methylation was significantly decreased in ovaries after exposed to BPA for 7 days, and testes following 35-day exposure. Moreover, the global level of DNA methylation was also significantly reduced in testes after exposed to 15μg/L BPA for 7 days. Besides the alteration of the global level of DNA methylation, varying degrees of transcriptional changes of dnmts, gnmt and tets were detected in gonads of D. rerio under BPA exposure. The present study suggested that BPA might cause the global DNA demethylation in gonads of zebrafish by regulating the transcriptional changes of the DNA methylation/demethylation-associated genes (dnmts, gnmt, and tets).

http://www.ncbi.nlm.nih.gov/pubmed/27101439

“Our data suggested **both Endocrine disruptors present potential for disrupting the structure and maintenance of the human blood-testis barrier** by Androgen Receptor dependent pathway.”

Toxicology In Vitro • August 2016

Regulatory and junctional proteins of the blood-testis barrier in human Sertoli cells are modified by monobutyl phthalate (MBP) and bisphenol A (BPA) exposure

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Abstract

The blood-testis barrier (BTB) is responsible for providing a protected environment and coordinating the spermatogenesis. Endocrine disruptors (EDs) might lead to infertility, interfering in the BTB structure and modulation. This study aimed to correlate the actions of two EDs, monobutyl phthalate (MBP) and bisphenol A (BPA) in different periods of exposure, in a low toxicity dose to the human Sertoli cells (HSeC) and its effects on the proteins of the BTB and regulatory proteins involved in its modulation. HSeC cells were exposed to MBP (10µM) and BPA (20µM) for 6 and 48h. Western Blot assay indicated that MBP was able to reduce the expression of occludin, ZO-1, N-cadherin and Androgen Receptor (AR), while BPA leads to a reduction of occludin, ZO-1, ß-catenin and AR. TGF-ß2 and F-actin were not modified. Phalloidin and Hematoxylin and Eosin assay revealed phenotically disruption in Sertoli cells adhesion, without changes in F-actin expression or localization. Our data suggested both EDs present potential for disrupting the structure and maintenance of the human BTB by AR dependent pathway.

http://www.ncbi.nlm.nih.gov/pubmed/26922907

Chemosphere • September 2016

From BPA to its analogues: Is it a safe journey?

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Abstract

“**Bisphenol-A (BPA) is one of the most abundant synthetic chemicals in the world due to its uses in plastics. Its widespread exposure vis-a-vis low dose effects led to a reduction in its safety dose and imposition of ban on its use in infant feeding bottles. This restriction paved the way for the gradual market entry of its analogues. However, their structural similarity to BPA has put them under surveillance for endocrine disrupting potential. The application of these analogues is increasing and so are the studies reporting their toxicity.** This review highlights the reasons which led to the ban of BPA and also reports the exposure and toxicological data available on its analogues. Hence, this compilation is expected to answer in a better way whether the replacement of BPA by these analogues is safer or more harmful?”

http://www.ncbi.nlm.nih.gov/pubmed/27262103

“This is the first report describing Bisphenol S and Bisphenol F adverse effects on a physiologic function in humans and rodents.”

Fertility And Sterility • January 2015

A new chapter in the bisphenol A story: bisphenol S and bisphenol F are not safe alternatives to this compound

Author information

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Abstract

Bisphenol A (BPA) is a widely studied typical endocrine-disrupting chemical, and one of the major new issues is the safe replacement of this commonly used compound. Bisphenol S (BPS) and bisphenol F (BPF) are already or are planned to be used as BPA alternatives. With the use of a culture system that we developed (fetal testis assay [FeTA]), we previously showed that 10 nmol/L BPA reduces basal testosterone secretion of human fetal testis explants and that the susceptibility to BPA is at least 100-fold lower in rat and mouse fetal testes. Here, we show that addition of LH in the FeTA system considerably enhances BPA minimum effective concentration in mouse and human but not in rat fetal testes. Then, using the FeTA system without LH (the experimental conditions in which mouse and human fetal testes are most sensitive to BPA), we found that, as for BPA, 10 nmol/L BPS or BPF is sufficient to decrease basal testosterone secretion by human fetal testes with often nonmonotonic dose-response curves. In fetal mouse testes, the dose-response curves were mostly monotonic and the minimum effective concentrations were 1,000 nmol/L for BPA and BPF and 100 nmol/L for BPS. Finally, 10,000 nmol/L BPA, BPS, or BPF reduced Insl3 expression in cultured mouse fetal testes. This is the first report describing BPS and BPF adverse effects on a physiologic function in humans and rodents.

Full text, free PDF, charts, graphs and 96 references

http://www.fertstert.org/article/S0015-0282(14)02351-6/pdf

Medicine (Baltimore) • January 2015

Bisphenol A and hormone-associated cancers: current progress and perspectives

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Abstract

Bisphenol A (BPA), a carbon-based synthetic compound, exhibits hormone-like properties and is present ubiquitously in the environment and in human tissues due to its widespread use and biological accumulation. BPA can mimic estrogen to interact with estrogen receptors alpha and beta leading to changes in cell proliferation, apoptosis, or migration and thereby, contributing to cancer development and progression. At the genetic level, BPA has been shown to be involved in multiple oncogenic signaling pathways, such as the STAT3, MAPK, and PI3K/AKT pathways. Moreover, BPA may also interact with other steroid receptors (such as androgen receptor) and plays a role in prostate cancer development. **This review summarizes the current literature regarding human exposure to BPA, the endocrine-disrupting effects of BPA, and the role of BPA in hormone-associated cancers of the breast, ovary, and prostate.**

Full text, schematic illustration and 122 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4602822/

BPA harms dental enamel in young animals, mimicking human tooth defect

San Diego, CA — A tooth enamel abnormality in children, molar incisor hypomineralization (MIH), may result from exposure to the industrial chemical bisphenol A (BPA), authors of a new study conclude after finding similar damage to the dental enamel of rats that received BPA. The study results will be presented Friday at the Endocrine Society's 97th annual meeting in San Diego.

"Human enamel defects may be used as an early marker of exposure to BPA and similar-acting endocrine disruptors," Babajko said.

BPA is an endocrine disruptor, or hormone-altering chemical, that has been linked to numerous adverse health effects in humans. It appears in many plastic and resin household products and food containers, including until recently baby bottles, sippy cups and infant formula packages.

Dental enamel is the hard covering protecting the teeth. MIH causes white or brown opaque spots on an affected child's permanent first molars and incisors (the middle four teeth on the top and bottom), which become sensitive, painful and prone to cavities. Recent published data show that MIH affects up to 18 percent of children ages 6 to 9 years. Although the cause is unclear, it appears to have an environmental origin, according to the study authors. In the first part of the study, Sylvie Babajko, PhD, a researcher at the French National Institute of Health and Medical Research (INSERM) in Paris, and her colleagues gave rats low doses of BPA, comparable to exposure in humans. The rats received BPA from fetal life to 30 days after birth. She said BPA caused enamel defects similar to MIH in humans, especially in male rats.

In part 2 of the study, the investigators cultured and looked at rat ameloblast cells, which are present only during the formation of tooth enamel, called amelogenesis. In humans, amelogenesis takes place from the third trimester of fetal development to 3 or 4 years after birth. This cell-based experiment showed that sex hormones target and influence dental epithelial cells.

"Our study shows, for the first time, that BPA affects dental cells, and subsequently enamel synthesis, using similar target molecules as those present in other organs," Babajko said.

She explained that these molecules are receptors for sex steroid hormones involved in organ development, endocrine homeostasis and hormone-sensitive cancers.

Babajko reported that an increase in estrogen activity had a greater effect on the tooth enamel in male rats than in female rats. This finding, she said, suggests possible sexual differences in enamel quality.

This work was funded by INSERM, the University Paris-Diderot and the French Institute of Odontological Research (IFRO).

ENDOCRINE SOCIETY
Hormone Science to Health

"Our study shows, for the first time, that **BPA affects dental cells**, and subsequently enamel synthesis, using similar target molecules as those present in other organs."

http://www.eurekalert.org/pub_releases/2015-03/tes-bhd030615.php

“The altered synaptic activity may implicate for **neurobehavioral locomotor abnormalities after exposure to BPA.**”

Neuroscience • March 2015

Bisphenol A depresses monosynaptic and polysynaptic reflexes in neonatal rat spinal cord in vitro involving estrogen receptor-dependent NO-mediated mechanisms

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Abstract

Bisphenol A (BPA), a toxic chemical from plastics, is known to produce locomotor abnormalities which may imply the alteration in synaptic activity at Ia-alpha motoneuron synapse also. However the effect of BPA on this synapse is not known. Therefore, this study was undertaken to examine the effect of BPA on reflexes originating at Ia-alpha motoneuron synapse in the spinal cord. The experiments were performed on isolated hemisected spinal cords from 4 to 6d rats. Stimulation of a dorsal root evoked segmental monosynaptic (MSR) and polysynaptic (PSR) reflex potentials in the corresponding ventral root. Nitrite content (indicator of NO activity) of cords was estimated in the presence of BPA with/without antagonists. Superfusion of BPA (3-100µM) depressed the reflexes in a concentration- and time-dependent manner. The depression was ~20, ~50 and ~70% at 10, 30 and 100µM of BPA, respectively. The 50% depression occurred around 15min at 30µM of BPA. Pretreatment with estrogen receptor (ERalpha) antagonist, tamoxifen, blocked the BPA-induced depression of reflexes, whereas, 17ß-estradiol, ER agonist, did not depress the reflexes even up to 10µM. Further, pretreatment with Nß-Nitro-l-arginine methyl ester hydrochloride (l-NAME) or hemoglobin (Hb) blocked the BPA-induced depression of spinal reflexes. Nitric oxide (NO) donor sodium-nitroprusside depressed the MSR and PSR in a concentration-dependent manner. The nitrite concentration of the cords exposed to BPA was 733µM/gm of tissue (three times the saline group). Pretreatment with tamoxifen/l-NAME/Hb blocked the BPA-induced increase of nitrite levels. The present observations indicate that BPA depressed spinal synaptic transmission through ER-alpha-dependent NO-mediated mechanisms. The altered synaptic activity may implicate for neurobehavioral locomotor abnormalities after exposure to BPA.

http://www.ncbi.nlm.nih.gov/pubmed/25595991

“This study provides **evidence of the induction of nitrosative stress by prenatal BPA in both the mother and fetus at time of birth** and is thus supportive of the use of maternal 3-nitrotyrosine as a biomarker for offspring health.”

Endocrinology • March 2015

Impact of gestational bisphenol A on oxidative stress and free fatty acids: Human association and interspecies animal testing studies

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Abstract

Bisphenol A (BPA) is a high production volume chemical and an endocrine disruptor. Developmental exposures to BPA have been linked to adult metabolic pathologies, but the pathways through which these disruptions occur remain unknown. This is a comprehensive interspecies association vs causal study to evaluate risks posed by prenatal BPA exposure and to facilitate discovery of biomarkers of relevance to BPA toxicity. Samples from human pregnancies during the first trimester and at term, as well as fetal and/or adult samples from prenatally BPA-treated sheep, rats, and mice, were collected to assess the impact of BPA on free fatty acid and oxidative stress dynamics. Mothers exposed to higher BPA during early to midpregnancy and their matching term cord samples displayed increased 3-nitrotyrosine (NY), a marker of nitrosative stress. Maternal samples had increased palmitic acid, which was positively correlated with NY. Sheep fetuses and adult sheep and rats prenatally exposed to a human-relevant exposure dose of BPA showed increased systemic nitrosative stress. The strongest effect of BPA on circulating free fatty acids was observed in adult mice in the absence of increased oxidative stress. This is the first multispecies study that combines human association and animal causal studies assessing the risk posed by prenatal BPA exposure to metabolic health. This study provides evidence of the induction of nitrosative stress by prenatal BPA in both the mother and fetus at time of birth and is thus supportive of the use of maternal NY as a biomarker for offspring health.

http://www.ncbi.nlm.nih.gov/pubmed/25603046

“The present results indicate that plastic boiled water [water containing BPA] **attenuates the protective cardio-respiratory reflexes and also produces histopathological changes in lungs.**”

Indian Journal Of Physiology And Pharmacology • April 2015

Toxic Chemical from Plastics Attenuates Phenylbiguanide-induced Cardio-respiratory Reflexes in Anaesthetized Rats

By Pant J, Pant MK, Chouhan S, Singh SP and Deshpande SB.

Abstract

Bisphenol A (BPA) attenuated phenylbiguanide (PBG)-induced cardio-respiratory reflexes involving decreased vagal afferent activity. BPA leaches out from plastics thus it is expected that chronic exposure to plastic boiled (PBW) water will also produce similar changes. Therefore, the present study was undertaken to evaluate the effects of chronic ingestion of PBW on PBG evoked reflexes and were compared with BPA. Adult female rats were ingested BPA containing pellets (2 µg/kg body weight)/PBW/tap water (ad libitum) for 30 days. On day 30, the animals were anaesthetized and BP, ECG and respiratory excursions were recorded. Further, PBG was injected intravenously to evoke cardio-respiratory reflexes and at the end lungs were excised for histopathological examination. BPA concentration in PBW was 6.6 µg/ml estimated by HPLC. In rats receiving tap water, PBG produced bradycardia, hypotension and tachypnoea. In PBW/BPA treated groups, PBG-induced reflexes were attenuated significantly along with emphysematous and consolidative changes in lungs. The present results indicate that PBW attenuates the protective cardio-respiratory reflexes and also produces histopathological changes in lungs.

http://www.ncbi.nlm.nih.gov/pubmed/26685510

“Exposure to BPA may be associated with **recurrent miscarriage risk**. Compared to the groups with ... levels less ... the women with levels ... above had a significantly higher risk of recurrent miscarriage ... **that persisted after adjusting for confounding factors.**”

PLoS One • May 2015

Higher urinary bisphenol A concentration is associated with unexplained recurrent miscarriage risk: evidence from a case-control study in eastern China

Author information

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Abstract

BACKGROUND

Evidence about the association between Bisphenol A (BPA) and the risk of recurrent miscarriage (RM) in human being is still limited.

OBJECTIVE

We evaluated the association of urinary BPA concentrations with RM in human being.

METHODS

A hospital-based 1:2 matched case-control study on RM was carried out in Suzhou and Kunshan in Jiangsu Province in China between August 2008 and November 2011. Total urinary BPA concentrations in 264 eligible urine samples (102 RM patients and 162 controls) were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The Wilcoxon test and conditional logistic regression were used to estimate the differences between the groups and odds ratios (OR) with 95% confidence intervals (CI), respectively.

RESULTS

The median ± IQR (interquartile range) (P75-P25) values of non-creatinine-adjusted total urinary BPA levels in the RM patients and the controls were 1.66 ± 3.69 ng/ml and 0.58 ± 1.07 ng/ml, respectively (0.98 ± 2.67 μg/g Cr (creatinine) and 0.40 ± 0.77 μg/g Cr. The adjusted BPA level was significantly higher in the RM patients than in the controls (Wilcoxon test, $Z = 4.476$, $P < 0.001$). Higher level of urinary BPA was significantly associated with an increased risk of RM (P-trend < 0.001). Compared to the groups with urinary BPA levels less than 0.16 μg/g Cr, the women with levels of 0.40-0.93 μg/g Cr and 0.93 μg/g Cr or above had a significantly higher risk of RM (OR = 3.91, 95%CI: 1.23-12.45 and OR = 9.34, 95%CI: 3.06-28.44) that persisted after adjusting for confounding factors. The time from recently RM date to recruitment does not significantly influence the urinary BPA level ($P = 0.090$).

CONCLUSION

Exposure to BPA may be associated with RM risk.

Full text, graphs, charts and 58 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4444137/

“Our results suggest that **urinary BPA levels are significantly associated with overweight in elderly women** but not elderly men.”

Environmental Science And Pollution Research International • June 2015

Association of bisphenol A exposure with overweight in the elderly: a panel study

Author information

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Abstract

Bisphenol A (BPA) is an ubiquitous chemical, which is an endocrine disruptor. Recent epidemiological studies have suggested a relationship between BPA exposure and body weight. However, most of these studies were cross-sectional and not on elderly people. We conducted a panel study with repeated measurements to evaluate the relationship between BPA and overweight in elderly people. A total of 560 elderly participants aged ≥60 years were recruited in Seoul from 2008 to 2010. Urinary BPA levels and body mass index (BMI, kg/m(2)) were measured at every visit. We defined a BMI ≥25 as overweight and examined the relations between urinary BPA and BMI or overweight. Repeated measures analysis was performed after adjusting for age, sex, low-density lipoprotein cholesterol levels, alcohol consumption, regular exercise, total calorie intake, fatty acid intake, urinary cotinine levels, and the status of diabetes mellitus. The geometric mean of BPA was 0.67 μg/g creatinine. The odds ratio (OR) of overweight was 1.17 (95 % confidence interval [CI] 1.04-1.32) per interquartile range increase of log-transformed BPA. When stratified based on sex, we observed a significant association in women (OR 1.25; 95 % CI 1.09-1.45) but not in men (OR 0.97; 95 % CI 0.77-1.22). The ORs of overweight increased with quartiles of BPA in women (quartile 2 vs 1: OR 1.54; 95 % CI 1.02-2.32, 3 vs 1: OR 1.70; 95 % CI 1.10-2.62, and 4 vs 1: OR 1.81; 95 % CI 1.13-2.92). Our results suggest that urinary BPA levels are significantly associated with overweight in elderly women but not elderly men.

http://www.ncbi.nlm.nih.gov/pubmed/25874422

“Bisphenol A (BPA), a known endocrine disruptor, is a food contaminant **suspected of being a contributing factor to the present-day increase in obesity, diabetes, and cardiovascular disease.**”

Dose Response • July 2015

Human Bisphenol A Exposure and the “Diabesity Phenotype”

Author information

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Abstract

Bisphenol A (BPA), a known endocrine disruptor, is a food contaminant suspected of being a contributing factor to the present-day increase in obesity, diabetes, and cardiovascular disease. This issue is of increasing interest in the field of diabetes research and has become a matter of concern for regulatory agencies and food industries. Recently, the number of studies involving BPA has increased exponentially, but there are still many gaps in the knowledge of the relationship between actual BPA exposure and cardiometabolic risk and of the modalities of food intake exposure, all of which prevents sound judgments concerning the risks to human health. This review focuses on the association between human exposure to BPA and obesity, thyroid function, diabetes, insulin resistance, metabolic syndrome, cardiovascular diseases, and BPA content in food. Many cross-sectional studies support, sometimes contradictorily, an adverse effect of BPA exposure on obesity, diabetes, and cardiovascular diseases. Few prospective studies support an adverse effect of BPA exposure on such pathologies. Moreover, no intervention studies have been conducted to evaluate the causality of such associations. This is mainly due to lack of an appropriate database of BPA content in foods, thus hindering any estimation of the usual dietary BPA intake.

Full text, graphs, charts and 107 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4734317/

“The results of the present study suggest **altered or disrupted ovulation.**”

Analytical And Quantitative Cytopathology And Histopathology • August 2015

Light and Transmission Electron Microscopic Studies on Subacute Toxicity of Bisphenol A on the Rat Ovary

By SY Saddick

Abstract

OBJECTIVE

To investigate subacute toxicity of Bisphenol A (BPA) in adult rat ovaries using gastric intubation daily for 4 weeks by light and transmission electron microscopy.

STUDY DESIGN

Fifteen rats were included in the study and divided into 2 groups: 12 rats were used for BPA administration (600 mg/kg body weight), and 3 rats received only vehicle and served as controls. The ovaries of both treated and control rats were taken at 1, 2, 3, and 4 weeks postadministration, fixed in 10% neutral buffered formalin, and processed for light microscopy. Ovarian samples at the 4th week postexposure were fixed in 3% glutaraldehyde and processed for transmission electron microscopy.

RESULTS

The main histopathological alterations were observed at the 3rd and 4th weeks postexposure. Atretic follicles,formation of cysts, separation of granulosa cells, and hyperemia of blood vessels were observed. Moreover, a marked increase in the thickness of the tunica albuginea was determined (33.8 ± 1.72 µm and 34.8 ± 1.72 µm, respectively,for the 3rd and 4th weeks as compared to the control group (13.78 ± 0.12 µm). Transmission electron microscopy showed marked lipid droplet accumulation, chromatin condensation in the nuclei of granulosa cells, and presence of autophagosomes in the treated group at 4 weeks postexposure as compared to the nonexposed group (control group).

CONCLUSION

The results of the present study suggest altered or disrupted ovulation. Moreover, change in the thickness of the tunica albuginea observed during the course of exposure may play a role in such disrupted ovulation.

http://www.ncbi.nlm.nih.gov/pubmed/26410969

“The single meal doses modeled in this research are at the same order of magnitude as the low-dose toxicity thresholds, **illustrating the potential for school meals to expose children to chronic toxic levels of BPA.**”

Journal Of Exposure Science & Environmental Epidemiology • September 2015

Probabilistic modeling of school meals for potential bisphenol A (BPA) exposure

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Abstract

Many endocrine-disrupting chemicals (EDCs), including bisphenol A (BPA), are approved for use in food packaging, with unbound BPA migrating into the foods it contacts. Children, with their developing organ systems, are especially susceptible to hormone disruption, prompting this research to model the potential dose of BPA from school-provided meals. Probabilistic exposure models for school meals were informed by mixed methods. Exposure scenarios were based on United States school nutrition guidelines and included meals with varying levels of exposure potential from canned and packaged food. BPA exposure potentials were modeled with a range of 0.00049 µg/kg-BW/day for a middle school student with a low exposure breakfast and plate waste to 1.19 µg/kg-BW/day for an elementary school student eating lunch with high exposure potential. The modeled BPA doses from school meals are below the current US EPA Oral Reference Dose (RfD) of 50 µg/kg-BW/day. Recent research shows BPA animal toxicity thresholds at 2 µg/kg-BW/day. The single meal doses modeled in this research are at the same order of magnitude as the low-dose toxicity thresholds, illustrating the potential for school meals to expose children to chronic toxic levels of BPA.

http://www.ncbi.nlm.nih.gov/pubmed/26395857

“... significant changes in geometric mean concentrations of BPA and BPS suggest that **exposures may be declining (BPA) or on the rise (BPS)** ...”

Environmental Science And Technology • October 2015

Urinary Concentrations of Bisphenol A and Three Other Bisphenols in Convenience Samples of U.S. Adults during 2000-2014

Author information

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Abstract

Because of regulatory actions and public concerns, the use of bisphenol A (BPA) may decrease, while the use of BPA alternatives may increase. Although BPA alternatives are considered safer than BPA, their effects on health are still largely unknown. For risk assessment, understanding exposure to these chemicals is necessary. We measured the urinary concentrations of BPA and three bisphenol analogs, bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF), in 616 archived samples collected from convenience samplings of U.S. adults at eight time points between 2000 and 2014. We detected BPA at the highest frequency and geometric mean (GM) concentrations (74-99%, 0.36-2.07 µg/L), followed by BPF (42-88%, 0.15-0.54 µg/L) and BPS (19-74%, < 0.1-0.25 µg/L); BPAF was rarely detected (<3% of all samples). Although concentrations of BPF were generally lower than for other bisphenols, the 95th percentile concentration of BPF was often comparable or higher than that of BPA. We did not observe obvious exposure trends for BPF. However, the significant changes in GM concentrations of BPA and BPS suggest that exposures may be declining (BPA) or on the rise (BPS). Nationally representative data will be useful to confirm these findings and to allow monitoring future exposure trends to BPA and some of its bisphenol alternatives.

http://www.ncbi.nlm.nih.gov/pubmed/26360019

“BPA or isobutylparaben (IBP) alone also **reduced epididymal sperm count and motility** compared to control. These results indicate that exposure to low-level BPA/IBP mixture, which showed no notable physiological response in early life stages, **can decrease semen quality in adulthood**.”

Human And Experimental Toxicology • October 2015

Reduction in semen quality after mixed exposure to bisphenol A and isobutylparaben in utero and during lactation periods

Author information

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Abstract

This study was performed to determine the effect of low-level exposure to a mixture of bisphenol A (BPA) and isobutylparaben (IBP) on male reproduction. Corn oil, BPA (0.05 mg/kg/day), IBP (2.5 mg/kg/day), and a BPA/IBP mixture (BPA 0.05 mg/kg/day and IBP 2.5 mg/kg/day) were administered once daily by oral gavage to female rats for 5 weeks from gestation day 6 to lactation day 21. Male pups were killed at postnatal day 70 and examined for developmental characteristics, body weight, testis and epididymis weight, steroid hormones, epididymal sperm count and motility, and histological changes in testis and epididymis. The BPA/IBP mixture produced a significant downregulation of epididymal sperm count and motility. BPA or IBP alone also reduced epididymal sperm count and motility compared to control. These results indicate that exposure to low-level BPA/IBP mixture, which showed no notable physiological response in early life stages, can decrease semen quality in adulthood.

http://www.ncbi.nlm.nih.gov/pubmed/26519482

“The reported findings identify the pancreatic islet as the main target of BPA toxicity in impairing the glycemia. They suggest that the **BPA exposure can weaken the response of the pancreatic islets to damages**.”

Cell Death And Disease • October 2015

Evaluation of low doses BPA-induced perturbation of glycemia by toxicogenomics points to a primary role of pancreatic islets and to the mechanism of toxicity

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Abstract

Epidemiologic and experimental studies have associated changes of blood glucose homeostasis to Bisphenol A (BPA) exposure. We took a toxicogenomic approach to investigate the mechanisms of low-dose (1 × 10(-9)M) BPA toxicity in ex vivo cultures of primary murine pancreatic islets and hepatocytes. Twenty-nine inhibited genes were identified in islets and none in exposed hepatocytes. Although their expression was slightly altered, their impaired cellular level, as a whole, resulted in specific phenotypic changes. Damage of mitochondrial function and metabolism, as predicted by bioinformatics analyses, was observed: BPA exposure led to a time-dependent decrease in mitochondrial membrane potential, to an increase of ROS cellular levels and, finally, to an induction of apoptosis, attributable to the bigger Bax/Bcl-2 ratio owing to activation of NF-κB pathway. Our data suggest a multifactorial mechanism for BPA toxicity in pancreatic islets with emphasis to mitochondria dysfunction and NF-κB activation. Finally, we assessed in vitro the viability of BPA-treated islets in stressing condition, as exposure to high glucose, evidencing a reduced ability of the exposed islets to respond to further damages. The result was confirmed in vivo evaluating the reduction of glycemia in hyperglycemic mice transplanted with control and BPA-treated pancreatic islets. The reported findings identify the pancreatic islet as the main target of BPA toxicity in impairing the glycemia. They suggest that the BPA exposure can weaken the response of the pancreatic islets to damages. The last observation could represent a broader concept whose consideration should lead to the development of experimental plans better reproducing the multiple exposure conditions.

http://www.ncbi.nlm.nih.gov/pubmed/26512966

“Bisphenol A (BPA) is an environmental endocrine disruptor that **has been associated with cardiovascular outcomes** in previous observational studies. In contrast with previous investigations, our study suggests negative associations of BPA exposure with **hypertension and early macrovascular diseases** among middle-aged and elderly Chinese.”

Medicine (Baltimore) • October 2015

Association of Bisphenol A Exposure With Hypertension and Early Macrovascular Diseases in Chinese Adults: A Cross-Sectional Study

Author information
Wang T1, Xu M, Xu Y, Lu J, Li M, Chen Y, Wang W, Lai S, Bi Y, Ning G.

Abstract

Bisphenol A (BPA) is an environmental endocrine disruptor that has been associated with cardiovascular outcomes in previous observational studies. We aimed to examine the relationships of urinary BPA levels with hypertension and early macrovascular diseases.

This is a cross-sectional study. From June through August 2009, 3246 participants ages 40 years or older were enrolled from Baoshan District, Shanghai, China. Logistic regression modes were used to estimate the odds ratios (ORs) for prevalent risk of hypertension, elevated carotid intima-media thickness (CIMT), arterial stiffness, and peripheral artery disease (PAD) with multivariable adjustment. We also performed stratification analysis by age and sex.

The median (interquartile range) for BPA was 0.81 (0.48, 1.45) ng/mL, which is notably lower than previously reported in the United States and other Western countries. Urinary BPA concentrations were negatively associated with hypertension (multivariable-adjusted OR for the highest versus lowest BPA quartile=0.61; 95% confidence interval [CI]: 0.46, 0.80), elevated CIMT (OR=0.64; 95% CI: 0.47, 0.87), and arterial stiffness (OR=0.62; 95% CI: 0.44, 0.87). The corresponding OR for PAD (60 cases total) was not significant (OR=0.89; 95% CI: 0.28, 2.80). The negative associations of BPA with hypertension, elevated CIMT, and arterial stiffness were consistent by age and sex stratifications, and were stronger among participants ≥60 versus <60 years of age, and among women than men.

In contrast with previous investigations, our study suggests negative associations of BPA exposure with hypertension and early macrovascular diseases among middle-aged and elderly Chinese. Future investigations are needed to draw more definite conclusions and generalize to other populations.

Full text with 42 references

http://journals.lww.com/md-journal/Fulltext/2015/10270/Association_of_Bisphenol_A_Exposure_With.35.aspx

“Here, we used the toxicant **Bisphenol A (BPA), a chemical known as a hazard to infants and children**, and showed that our stem cell toxicology system was able to efficiently recapitulate most of the toxic effects of BPA previously detected by in vitro system or animal tests.”

Journal Of Environmental Science (China) • October 2015

Assessment of Bisphenol A (BPA) neurotoxicity in vitro with mouse embryonic stem cells

Author information

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Abstract

The adverse effects of environmental pollution on our well-being have been intensively studied with many in vitro and in vivo systems. In our group, we focus on stem cell toxicology due to the multitude of embryonic stem cell (ESC) properties which can be exerted in toxicity assays. In fact, ESCs can differentiate in culture to mimic embryonic development in vivo, or specifically to virtually any kind of somatic cells. Here, we used the toxicant Bisphenol A (BPA), a chemical known as a hazard to infants and children, and showed that our stem cell toxicology system was able to efficiently recapitulate most of the toxic effects of BPA previously detected by in vitro system or animal tests. More precisely, we demonstrated that BPA affected the proper specification of germ layers during our in vitro mimicking of the embryonic development, as well as the establishment of neural ectoderm and neural progenitor cells.

http://www.ncbi.nlm.nih.gov/pubmed/26456621

“BPA treatment also caused a significant increase in serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase indicating its potential hepatotoxicity. Furthermore, histopathological findings revealed **marked edema formation, hepatocellular degeneration, and necrosis of liver tissue** in BPA-exposed rats.”

Environmental Toxicology • October 2015

Mitochondrial dysfunction induced by Bisphenol A is a factor of its hepatotoxicity in rats

Author information

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Abstract

Bisphenol A (BPA), an estrogenic and endocrine disrupting agent, is widely used in manufacturing of polycarbonate plastics and epoxy resins. BPA and other endocrine disrupting chemicals (EDCs) act via multiple mechanisms including interference with mitochondrial functions. Mitochondria are the hub of cellular energy pool and hence are the target of many EDCs. We studied perturbation of activities of mitochondrial enzymes by BPA and its possible role in hepatotoxicity in Wistar rats. Rats were exposed to BPA (150 mg/kg, 250 mg/kg, 500 mg/kg per os, for 14 days) and activities of enzymes of mitochondrial electron transport chain (ETC) were measured. Besides, other biochemical parameters such as superoxide generation, protein oxidation, and lipid peroxidation (LPO) were also measured. Our results indicated a significant decrease in the activities of enzymes of mitochondrial ETC complexes, i.e., complex I, II, III, IV, and V along with significant increase in LPO and protein oxidation. Additionally, a significant increase in mitochondrial superoxide generation was also observed. All these findings could be attributed to enhanced oxidative stress, decrease in reduced glutathione level, and decrease in the activity of superoxide dismutase in rat liver mitochondria isolated from BPA-treated rats. BPA treatment also caused a significant increase in serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase indicating its potential hepatotoxicity. Furthermore, histopathological findings revealed marked edema formation, hepatocellular degeneration, and necrosis of liver tissue in BPA-exposed rats. In conclusion, this study provides an evidence of impaired mitochondrial bioenergetics and liver toxicity after high-dose BPA exposure in rats.

http://www.ncbi.nlm.nih.gov/pubmed/26450347

“... the increasing incidence of developmental disorders is of concern, and accumulating evidence indicates that **BPA has detrimental effects on neurological development. Other bisphenol analogues, used as substitutes for BPA, are also suspected of having a broad range of biological actions.**”

International Journal Of Medicinal Science • October 2015

Neurological Effects of Bisphenol A and its Analogues

Author information

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Abstract

The endocrine disrupting chemical bisphenol A (BPA) is widely used in the production of polycarbonate plastics and epoxy resins. The use of BPA-containing products in daily life makes exposure ubiquitous, and the potential human health risks of this chemical are a major public health concern. Although numerous in vitro and in vivo studies have been published on the effects of BPA on biological systems, there is controversy as to whether ordinary levels of exposure can have adverse effects in humans. However, the increasing incidence of developmental disorders is of concern, and accumulating evidence indicates that BPA has detrimental effects on neurological development. Other bisphenol analogues, used as substitutes for BPA, are also suspected of having a broad range of biological actions. The objective of this review is to summarize our current understanding of the neurobiological effects of BPA and its analogues, and to discuss preventive strategies from a public health perspective.

http://www.ncbi.nlm.nih.gov/pubmed/26664253

“Current findings suggest developmental exposure of rats to BPA **may disrupt aspects of spatial navigational learning and memory.**”

Hormones And Behavior • October 2015

Effects of developmental exposure to bisphenol A on spatial navigational learning and memory in rats: A CLARITY-BPA study

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SELECTED FEDERAL AGENCIES AND THEIR SPECIFIC ROLE IN FOOD SAFETY

Food Safety and Inspection Service (FSIS)

The Food Safety and Inspection Service (FSIS) is the public health agency in the U.S. Department of Agriculture responsible for ensuring that the nation's commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled and packaged.

U.S. Food and Drug Administration (FDA)

The FDA is charged with protecting consumers against impure, unsafe, and fraudulently labeled products. FDA, through its Center for Food Safety and Applied Nutrition (CFSAN), regulates foods other than the meat, poultry, and egg products regulated by FSIS. FDA is also responsible for the safety of human drugs, medical devices, biologics, animal feed and animal drugs, cosmetics and radiation emitting devices.

Centers for Disease Control and Prevention (CDC)

CDC leads federal efforts to gather data on foodborne illnesses, investigate foodborne illnesses and outbreaks, and monitor the effectiveness of prevention and control efforts in reducing foodborne illnesses. CDC also plays a key role in building state and local health department epidemiology, laboratory, and environmental health capacity to support foodborne disease surveillance and outbreak response.

USDA

Drugs And Medications Added To The Food Supply

When drugs and medications are re-named "food additives" and added to the entire global food supply in such an all-pervasive manner that they become ubiquitous, disease and disorder is not only imminent, it's now obvious. The human species has been genetically altered permanently, forever—there's no return from this system-wide poisoning. And this effects the children we haven't yet had.

It's The Food Additive Wild West

There are millions of super market-aisles across the globe stocked with "grab me" boxes, "I want you" jars and "gotta have" cans of mind-bending, endocrine system altering, neurological and behavior changing xenobiotics. We live in the Food Additive Wild West and the sheriff, the FDA, the USDA and the CDC, are bought and paid for, just like the Pinkerton's of the Wild West.

Abstract

Bisphenol A (BPA) is a ubiquitous industrial chemical used in the production of a wide variety of items. Previous studies suggest BPA exposure may result in neuro-disruptive effects; however, data are inconsistent across animal and human studies. As part of the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA), we sought to determine whether female and male rats developmentally exposed to BPA demonstrated later spatial navigational learning and memory deficits. Pregnant NCTR Sprague-Dawley rats were orally dosed from gestational day 6 to parturition, and offspring were directly orally dosed until weaning (postnatal day 21). Treatment groups included a vehicle control, three BPA doses (2.5µg/kg body weight (bw)/day-[2.5], 25µg/kg bw/day-[25], and 2500µg/kg bw/day-[2500]) and a 0.5µg/kg/day ethinyl estradiol (EE)-reference estrogen dose. At adulthood, 1/sex/litter was tested for seven days in the Barnes maze. The 2500 BPA group sniffed more incorrect holes on day 7 than those in the control, 2.5 BPA, and EE groups. The 2500 BPA females were less likely than control females to locate the escape box in the allotted time (p value=0.04). Although 2.5 BPA females exhibited a prolonged latency, the effect did not reach significance (p value=0.06), whereas 2.5 BPA males showed improved latency compared to control males (p value=0.04), although the significance of this result is uncertain. No differences in serum testosterone concentration were detected in any male or female treatment groups. Current findings suggest developmental exposure of rats to BPA may disrupt aspects of spatial navigational learning and memory.

http://www.ncbi.nlm.nih.gov/pubmed/26436835

“The present findings suggest that dietary xenobiotic contamination can give rise to metabolic disorders also in fish and highlight the potential for their vertical transfer through the trophic levels **and ultimately to humans.**”

Aquatic Toxicology • October 2015

Xenobiotic-contaminated diets affect hepatic lipid metabolism: Implications for liver steatosis in Sparus aurata juveniles

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Abstract

The metabolic effects induced by feed contaminated with a lower or a higher concentration of -nonylpnenol (NP), 4-tert-octylphenol (t-OP) or bisphenol A (BPA), three environmental endocrine disruptors, were assessed in juvenile sea bream liver. Histological analysis demonstrated that all these three xenobiotics induced hepatic lipid accumulation and steatosis. These findings prompted analysis of the expression of the major molecules involved in lipid metabolism: peroxisome proliferator activated receptors (which is encoded by ppars), fatty acid synthase (encoded by fas), lipoprotein lipase (encoded by lpl) and hormone-sensitive lipase (encoded by hsl). The enzymes encoded by ppars and fas are in fact responsible for lipid accumulation, whereas lpl- and hsl- encoded proteins play a pivotal role in fat mobilization. The three xenobiotics modulated ppar mRNA expression: ppars mRNA expression was induced by the higher dose of each contaminant; ppar ßmRNA expression was upregulated by the lower doses and in BPA2 fish ppary mRNA overexpression was induced by all pollutants. These data agreed with the lipid accumulation profiles documented by histology. Fas mRNA levels were modulated by the two NP doses and the higher BPA concentration. Lpl mRNA was significantly upregulated in all experimental groups except for BPA1 fish while hsl mRNA was significantly downregulated in all groups except for t-OP2 and BPA1 fish. The plasma concentrations of cortisol, the primary stress biomarker, were correlated with the levels of pepck mRNA level. This gene encodes phosphoenolpyruvate carboxykinase which is one of the key enzymes of gluconeogenesis. Pepck mRNA was significantly overexpressed in fish exposed to NP2 and both t-OP doses. Finally, the genes encoding cyclooxygenase 2 (cox2) and 5-lipoxygenase (5 lox), the products of which are involved in the inflammatory response, transcriptions were significantly upregulated in NP and BPA fish, whereas they were unchanged in t-OP specimens. The present findings suggest that dietary xenobiotic contamination can give rise to metabolic disorders also in fish and highlight the potential for their vertical transfer through the trophic levels and ultimately to humans.

http://www.ncbi.nlm.nih.gov/pubmed/26382854

“These results suggest **BPA exposure may affect childhood behavioral outcomes** in a sex-specific manner and differently depending on timing of exposure.”

Environmental Research • October 2015

Bisphenol A exposure and behavioral problems among inner city children at 7-9 years of age

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http://www.ncbi.nlm.nih.gov/pubmed/25724466

Abstract

BACKGROUND

Bisphenol A (BPA) is a ubiquitous endocrine disrupting compound. Several experimental and epidemiological studies suggest that gestational BPA exposure can lead to neurodevelopmental and behavioral problems in early-life, but results have been inconsistent. We previously reported that prenatal BPA exposure may affect child behavior and differently among boys and girls at ages 3-5 years.

OBJECTIVES

We investigated the association of prenatal and early childhood BPA exposure with behavioral outcomes in 7-9 year old minority children and hypothesized that we would observe the same sex-specific pattern observed at earlier ages

.METHODS

African-American and Dominican women enrolled in an inner-city prospective cohort study and their children were followed from mother’s pregnancy through children’s age 7-9 years. Women during the third trimester of pregnancy and children at ages 3 and 5 years provided spot urine samples. BPA exposure was categorized by tertiles of BPA urinary concentrations. The Child Behavioral Checklist (CBCL) was administered at ages 7 and 9 to assess multiple child behavior domains. Associations between behavior and prenatal (maternal) BPA concentrations and behavior and postnatal (child) BPA concentration were assessed via Poisson regression in models stratified by sex. These models accounted for potential confounders including prenatal or postnatal urinary BPA concentrations, child age at CBCL assessment, ethnicity, gestational age, maternal intelligence, maternal education and demoralization, quality of child’s home environment, prenatal environmental tobacco smoke exposure, and prenatal mono-n-butyl phthalate concentration.

RESULTS

The direction of the associations differed between boys and girls. Among boys (n=115), high prenatal BPA concentration (upper tertile vs. lower two tertiles) was associated with increased internalizing (β=0.41, $p<0.0001$) and externalizing composite scores (β=0.40, $p<0.0001$) and with their corresponding individual syndrome scales. There was a general decrease in scores among girls that was significant for the internalizing composite score (β=-0.17, p=0.04) (n=135). After accounting for possible selection bias, the results remained consistent for boys. Conversely, high postnatal BPA concentration was associated with increased behaviors on both the internalizing composite (β=0.30, p=0.0002) and externalizing composite scores (β=0.33, $p<0.0001$) and individual subscores in girls but fewer symptoms in boys. These results remained significant in girls after accounting for selection bias.

CONCLUSION

These results suggest BPA exposure may affect childhood behavioral outcomes in a sex-specific manner and differently depending on timing of exposure.

“Bisphenol A (BPA) is among the most prominent environmental estrogens worldwide, demonstrated to be related with the impairment of male reproductive function as well as other health problems, such as diabetes, obesity, cardiovascular diseases, and cancer. BPA is also involved in DNA methylation and the effects of epigenetics, resulting in dyszoospermia, oligoasthenoteratospermia/azoospermia and/or infertility in males.”

Zhonghua Nan Ke Xue • November 2015

Male reproductive toxicity of bisphenol A

By WJ Zhu and J Qiao

Abstract

The reproductive toxicity of environmental endocrine disruptors has attracted substantial attention from researchers in recent years. Bisphenol A (BPA) is among the most prominent environmental estrogens worldwide, demonstrated to be related with the impairment of male reproductive function as well as other health problems, such as diabetes, obesity, cardiovascular diseases, and cancer. BPA acts primarily by mimicking antiandrogenic and estrogenic effects, disturbing the hypothalamic-pituitary-testicular axis and modulating gene expressions and enzyme activities in the hormone biosynthesis affecting steroids or its receptors. BPA is also involved in DNA methylation and the effects of epigenetics, resulting in dyszoospermia, oligoasthenoteratospermia/azoospermia and/or infertility in males. This review addresses the effects of BPA on male reproductive function, focusing on the mechanisms of its toxicity on spermatogenesis, semen quality, and the reproductive system.

http://www.ncbi.nlm.nih.gov/pubmed/26738332

“**The molecule leaches out into the food, increasingly if exposed to warm temperatures and high acidity**. BPA is known for many negative effects on the human body; for instance it acts as an xenoestrogen and **influences fertility and gestation** and might also have **carcinogenic effects, causing breast and prostate cancer**. Although it has not yet been proven as a direct cause of autoimmunity, many of the effects of BPA can be related to the pathogenesis of autoimmune disease.”

Harefuah • November 2015

Bisphenol A—An Infamous Molecule

By A. Gutman and Y. Shoenfeld

Abstract

Bisphenol A (BPA) is a monomer found in plastic products used daily for the storage and consumption of food and beverages, such as plastic bottles, containers, and even toys. The molecule leaches out into the food, increasingly if exposed to warm temperatures and high acidity. BPA is known for many negative effects on the human body; for instance it acts as an xenoestrogen and influences fertility and gestation and might also have carcinogenic effects, causing breast and prostate cancer. Although it has not yet been proven as a direct cause of autoimmunity, many of the effects of BPA can be related to the pathogenesis of autoimmune disease (AID). Its estrogenic behavior modulates the immune system, it encourages the secretion of Prolactin that is known to be associated to AID, it creates oxidative stress that triggers the immune system and so on. Therefore there is room to advise individuals at risk for AID to avoid the consumption of BPA, similar to guidelines for pregnant women.

http://www.ncbi.nlm.nih.gov/pubmed/26821503

“Our findings revealed that exposure to 1nM (0.228μg/L) BPA for continuous two generations resulted in female-biased sex ratio in both F1 and F2 adult population, **decreased sperm density, and decreased sperm quality** as measured by motility, velocity, adenosine triphosphate content and lipid peroxidation ...
In conclusion, low level BPA exposures for continuous two generations not only affects sex ratio and sperm quantity/quality in F1 and F2 adults, reproductive success in offspring from F2 parents, but also perturbs various molecular pathways potentially contributing to these **BPA induced male-specific reproductive defects.**”

Aquatic Toxicology • December 2015

Reproductive toxicity of low level bisphenol A exposures in a two-generation zebrafish assay: Evidence of male-specific effects

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Abstract

Bisphenol A (BPA), a high-volume chemical used to make polycarbonate plastic and epoxy resins, is a ubiquitous contaminant in environment and human body. To investigate the reproductive effects of long-term exposure to low concentrations of BPA, a two-generation study was conducted using the aquatic model species of zebrafish. Our findings revealed that exposure to 1nM (0.228μg/L) BPA for continuous two generations resulted in female-biased sex ratio in both F1 and F2 adult population, decreased sperm density, and decreased sperm quality as measured by motility, velocity, ATP content and lipid peroxidation in F1 and F2 males. Females were less sensitive to BPA exposures than males as no adverse effects were found in female gonads or gametes. Delayed hatching at 48hpf and increased malformation and mortality were found in the offspring from BPA exposed F2, but not F1 parents. Most importantly, the adverse effect on larval development and survival from BPA exposed F2 parents was paternal-specific, resulting mainly from BPA exposed males. Subsequent transcription analysis of F2 male gonads revealed dysregulated mitochondrial biogenesis and significant activation of non-canonical Wnt/planar cell polarity and Wnt/Calcium signaling pathways. Gene expression analysis of larvae from BPA exposed F2 parents showed significant reduced expression of DNA methyltransferases such as dnmt1, dnmt3, and dnmt5. In conclusion, low level BPA exposures for continuous two generations not only affects sex ratio and sperm quantity/quality in F1 and F2 adults, reproductive success in offspring from F2 parents, but also perturbs various molecular pathways potentially contributing to these BPA induced male-specific reproductive defects.

http://www.ncbi.nlm.nih.gov/pubmed/26562050

“BPA was found at a concentration in the range of several tens to several hundreds of nanograms per liter in most of the rivers surveyed and some of the highest concentrations (54-1950 ng/L) were found in rivers in Chennai, India. **Concentrations of BPF were one to two orders of magnitude higher than those of BPA** in river and sea waters collected from Japan, Korea and China, which suggested that BPF is a major contaminant in surface waters in several Southeast Asian countries.”

Ecotoxicology And Environmental Safety • December 2015

Bisphenol A and other bisphenol analogues including BPS and BPF in surface water samples from Japan, China, Korea and India

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Abstract

Concentrations of eight bisphenol analogues (BPs) including BPA, BPS, and BPF were determined in surface waters collected from select rivers in Japan, Korea, China, and India. BPA was found at a concentration in the range of several tens to several hundreds of nanograms per liter in most of the rivers surveyed and some of the highest concentrations (54-1950 ng/L) were found in rivers in Chennai, India. Concentrations of BPF were one to two orders of magnitude higher than those of BPA in river and sea waters collected from Japan, Korea and China, which suggested that BPF is a major contaminant in surface waters in several Southeast Asian countries. BPF concentrations as high as 2850 ng/L were found in the Tamagawa River in Japan. The flux of BPs through riverine discharges into Tokyo Bay was calculated to be approximately 5.5 t per year. Based on the flux estimates and the mass of BPF found in water column and sediment in Tokyo Bay, it was found that BPF degrades faster than BPA in the environment. Elevated concentrations of BPF found in surface waters suggest the need for further studies to determine the fate and toxicity of this compound.

http://www.ncbi.nlm.nih.gov/pubmed/26436777

“This study shows that the association of prenatal **exposure to BPA** with anthropometric measures, such as birth weight and birth length, **differed by gender**.”

International Journal Of Hygiene And Environmental Health • March 2014

Prenatal bisphenol A and birth outcomes: MOCEH (Mothers and Children’s Environmental Health) study

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Abstract

Bisphenol A (BPA) is used primarily in the production of polycarbonate plastics and epoxy resins. Widespread exposure to BPA has created a great deal of concern regarding its potential adverse effects on human health. This study examined the relationship between prenatal BPA exposure and birth outcomes, including birth weight, birth length, and ponderal index considering gender difference. A multi-center birth cohort study, Mothers and Children’s Environmental Health (MOCEH) has been established in Korea since 2006. Study subjects are 757 pregnant women from the original cohort, who had their urinary BPA level measured during the third trimester, as well as information on birth outcome, prior medical history, psychosocial status, health behavior, environmental exposure as well as socio-demographic characteristics. Regression analysis was performed to assess the effect of BPA on birth outcome. The geometric mean concentration of BPA in pregnant women was 1.29 μg/L (1.87 μg/g creatinine) during late pregnancy. Urinary BPA concentrations were shown to be higher in women with a higher income level. Univariate regression analysis revealed a significant association between BPA levels and birth weight. In adjusted analysis, the second tertile of maternal BPA exposure exhibited an increase in birth weight, relative to the first tertile ($p=0.04$). These relationships were more pronounced in male neonates. Also, prenatal exposure to BPA was associated with an increase of ponderal index in total, and especially female neonates. This study shows that the association of prenatal exposure to BPA with anthropometric measures, such as birth weight and birth length, differed by gender. Further study is required to more fully elaborate this relationship between prenatal BPA exposure and birth outcome.

http://www.ncbi.nlm.nih.gov/pubmed/23911140

“This hazard assessment survey showed that many BPA-free PC- replacement products still leached chemicals having significant levels of estrogenic activity (EA), as did BPA-containing polycarbonate counterparts they were meant to replace. **That is, BPA-free [still] did not mean estrogenic activity-free.**”

Environmental Health • March 2014

Estrogenic chemicals often leach from BPA-Free plastic products that are replacements for BPA-containing polycarbonate products

By George D. Bittner, Chun Z. Yang and Matthew A. Stoner

Abstract

Background

Xenobiotic chemicals with estrogenic activity (EA), such as bisphenol A (BPA), have been reported to have potential adverse health effects in mammals, including humans, especially in fetal and infant stages. Concerns about safety have caused many manufacturers to use alternatives to polycarbonate (PC) resins to make hard and clear, reusable, plastic products that do not leach BPA. However, no study has focused on whether such BPA-free PC-replacement products, chosen for their perceived higher safety, especially for babies, also release other chemicals that have EA.

Methods

We used two, well-established, mammalian cell-based, assays (MCF-7 and BG1Luc) to assess the EA of chemicals that leached into over 1000 saline or ethanol extracts of 50 un-stressed or stressed (autoclaving, microwaving, and UV radiation) BPA-free PC-replacement products. An EA antagonist, ICI 182,780, was used to confirm that agonist activity in leachates was due to chemicals that activated the mammalian estrogen receptor.

Results

Many unstressed and stressed, PC-replacement-products made from acrylic, polystyrene, polyethersulfone, and Tritan™ resins leached chemicals with EA, including products made for use by babies. Exposure to various forms of UV radiation often increased the leaching of chemicals with EA. In contrast, some BPA-free PC-replacement products made from glycol-modified polyethylene terephthalate or cyclic olefin polymer or co-polymer resins did not release chemicals with detectable EA under any conditions tested.

Conclusions

This hazard assessment survey showed that many BPA-free PC- replacement products still leached chemicals having significant levels of EA, as did BPA-containing PC counterparts they were meant to replace. That is, BPA-free did not mean EA-free. However, this study also showed that some PC-replacement products did not leach chemicals having significant levels of EA. That is, EA-free PC-replacement products could be made in commercial quantities at prices that compete with PC-replacement products that were not BPA-free. Since plastic products often have advantages (price, weight, shatter-resistance, etc.) compared to other materials such as steel or glass, it is not necessary to forgo those advantages to avoid release into foodstuffs or the environment of chemicals having EA that may have potential adverse effects on our health or the health of future generations.

Full text, PDF, graphs, charts and 25 references

http://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-13-41

“Endocrine disrupting chemicals (EDCs) **can interfere with normal hormonal balance** and may exert adverse consequences on humans. The male reproductive system may be susceptible to the effects of such environmental toxicants.”

Frontiers In Public Health • June 2014

Exposure to endocrine disrupting chemicals and male reproductive health

By Anna Jeng Hueiwang

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Abstract

Endocrine disrupting chemicals (EDCs) can interfere with normal hormonal balance and may exert adverse consequences on humans. The male reproductive system may be susceptible to the effects of such environmental toxicants. This review discusses the recent progress in scientific data mainly from epidemiology studies on the associations between EDCs and male reproductive health and our understanding of possible mechanisms associated with the effects of EDCs on male reproductive health. Finally, the review provides recommendations on future research to enhance our understanding of EDCs and male reproductive health. The review highlights the need for (1) well-defined longitudinal epidemiology studies, with appropriately designed exposure assessment to determine potential causal relationships; (2) chemical and biochemical approaches aimed at a better understanding of the mechanism of action of xenoestrogens with regard to low-dose effects, and assessment of identify genetic susceptibility factors associated with the risk of adverse effects following exposure to EDCs.

Full text, graphs, charts and 111 references

http://journal.frontiersin.org/article/10.3389/fpubh.2014.00055/full

Toxicology Science • July 2014

Investigation of the effects of subchronic low dose oral exposure to bisphenol A (BPA) and ethinyl estradiol (EE) on estrogen receptor expression in the juvenile and adult female rat hypothalamus

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Abstract

Concerns have been raised regarding the long-term impacts of early life exposure to the ubiquitous environmental contaminant bisphenol A (BPA) on brain organization. Because BPA has been reported to affect estrogen signaling, and steroid hormones play a critical role in brain sexual differentiation, there is also concern that BPA exposure could alter neural sex differences. Here, we examine the impact of subchronic exposure from gestation to adulthood to oral doses of BPA below the current no-observed-adverse-effect level (NOAEL) of 5 mg/kg body weight (bw)/day on estrogen receptor (ESR) expression in sexually dimorphic brain regions of prepubertal and adult female rats. The dams were gavaged daily with vehicle (0.3% carboxymethylcellulose), 2.5, 25, 260, or 2700 µg BPA/kg bw/day, or 0.5 or 5.0 µg ethinyl estradiol (EE)/kg bw/day from gestational day 6 until labor began. Offspring were then gavaged directly from the day after birth until the day before scheduled sacrifice on postnatal days 21 or 90. Using in situ hybridization, one or more BPA doses produced significant decreases in Esr1 expression in the juvenile female rat anteroventral periventricular nucleus (AVPV) of the hypothalamus and significant decreases in Esr2 expression in the adult female rat AVPV and medial preoptic area (MPOA), relative to vehicle controls. BPA did not simply reproduce EE effects, indicating that BPA is not acting solely as an estrogen mimic. The possible consequences of long-term changes in hypothalamic ESR expression resulting from subchronic low dose BPA exposure on neuroendocrine effects are discussed and being addressed in ongoing, related work.

Full text with 90 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4133590/

“Because BPA has been reported to affect estrogen signaling, and steroid hormones play a critical role in brain sexual differentiation, there is also concern that **BPA exposure could alter neural sex differences**.

The possible consequences of long-term changes in hypothalamic-estrogen receptor expression resulting from subchronic low dose BPA exposure on neuroendocrine effects are discussed and being addressed in ongoing, related work.”

“Recent epidemiological studies have shown that higher urinary BPA concentration in humans is associated with various types of Cardiovascular diseases, **including angina, hypertension, heart attack and coronary and peripheral arterial disease**.”

International Journal Of Environmental Research And Public Health • August 2014

Impact of bisphenol a on the cardiovascular system— epidemiological and experimental evidence and molecular mechanisms

Author information

By X Gao and H Wang

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Abstract

Bisphenol A (BPA) is a ubiquitous plasticizing agent used in the manufacturing of polycarbonate plastics and epoxy resins. There is well-documented and broad human exposure to BPA. The potential risk that BPA poses to the human health has attracted much attention from regulatory agencies and the general public, and has been extensively studied. An emerging and rapidly growing area in the study of BPA's toxicity is its impact on the cardiovascular (CV) system. Recent epidemiological studies have shown that higher urinary BPA concentration in humans is associated with various types of CV diseases, including angina, hypertension, heart attack and coronary and peripheral arterial disease. Experimental studies have demonstrated that acute BPA exposure promotes the development of arrhythmias in female rodent hearts. Chronic exposure to BPA has been shown to result in cardiac remodeling, atherosclerosis, and altered blood pressure in rodents. The underlying mechanisms may involve alteration of cardiac Ca2+ handling, ion channel inhibition/activation, oxidative stress, and genome/transcriptome modifications. In this review, we discuss these recent findings that point to the potential CV toxicity of BPA, and highlight the knowledge gaps in this growing research area.

Full text with 63 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4143868/

“Cytochrome P450 aromatase (CYP19A1A), is responsible for the conversion of androgens into estrogens, which plays a vital role in estrogen synthesis in gonads. In the present study, the methylation level of ovarian cyp19a1a gene was **significantly suppressed and stimulated** by 7- and 35-day BPA exposure, respectively.”

Aquatic Toxicology • November 2014

Global and cyp19a1a gene specific DNA methylation in gonads of adult rare minnow Gobiocypris rarus under bisphenol A exposure

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Abstract

As a weak estrogenic chemical, bisphenol A (BPA) has been extensively studied for reproductive toxicity and the effects on the steroidogenesis. In the present study, we aim to explore the effects of BPA on epigenetic modification in rare minnow Gobiocypris rarus. We have detected the global and cyp19a1a gene specific DNA methylation in gonads of adult G. rarus under BPA exposure. The global DNA methylation level was significantly increased in testis of the male fish exposed to BPA for 7 days, and it was significantly increased in the ovary following 35-days exposure. DNA methyltransferases (DNMTs) catalyze the transfer of a methyl moiety from S-adenosyl-l-methionine to the cytosine of a CpG dinucleotide. The alteration of the detected dnmts mRNA expression could affect the global DNA methylation levels following 15μg/L BPA exposure. Cytochrome P450 aromatase (CYP19A1A), is responsible for the conversion of androgens into estrogens, which plays a vital role in estrogen synthesis in gonads. In the present study, the methylation level of ovarian cyp19a1a gene was significantly suppressed and stimulated by 7- and 35-day BPA exposure, respectively. There was a significant negative correlation between cyp19a1a mRNA expression and methylation levels of the four CpGs at the 5’ flanking region in the ovary of adult G. rarus following BPA exposure. So we hypothesize that there are some association between the reproductive toxicity of BPA and the global DNA methylation under BPA exposure. And the alteration of cyp19a1a expression in female G. rarus by BPA might attribute to the change of its DNA methylation status.

http://www.ncbi.nlm.nih.gov/pubmed/25125231

“There is increasing evidence suggesting that **Bisphenol A (BPA), one of the highest volume chemicals produced worldwide, can interfere with the body’s natural weight control mechanisms to promote obesity.** Multiple linear regression analyses showed that urine BPA concentrations were significantly associated with increasing Body Mass Index values in all subjects after adjustment for age and sex ...”

Environmental Health • October 2014

Association between bisphenol A exposure and body mass index in Chinese school children: a cross-sectional study

Author information

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Key Laboratory of Public Health Safety of Ministry of Education, School of Public Health, Fudan University, Shanghai, 200032, China

Abstract

RESULTS

BPA was detected in 84.9% of urine samples with a geometric mean of 0.45 ng/mL. The daily intake estimates ranged from 0.03 μg/day to 1.96 μg/day with a geometric mean of 0.37 μg/day. The average urine BPA concentrations and daily intake estimates were similar for boys and girls, but significantly higher in older children than younger ones, and showed an increasing trend with BMI. Multiple linear regression analyses showed that urine BPA concentrations were significantly associated with increasing BMI values in all subjects after adjustment for age and sex and the results were similar before and after corrected by urine specific gravity. When stratified by age or sex, the associations remained significant in females and in those 8-11 years of age before corrected by specific gravity. Similar results were shown for the association between BMI and daily intake estimates.

CONCLUSIONS

There is a possibility that BPA exposure increases BMI in school children.
Given the cross-sectional nature of this study, longitudinal studies are warranted to confirm BPA exposure as a contributor to increased BMI in children.

Full text, graphs, charts and 52 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3549797/

“Prenatal and early-childhood BPA exposures were not associated with increased BMI at 2-5 years of age, but higher early-childhood BPA exposures were associated with **accelerated growth** during this period.”

Environmental Health Perspectives • November 2014

Early-life bisphenol a exposure and child body mass index: a prospective cohort study

Author information
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Abstract

BACKGROUND

Early-life exposure to bisphenol A (BPA) may increase childhood obesity risk, but few prospective epidemiological studies have investigated this relationship.

OBJECTIVE

We sought to determine whether early-life exposure to BPA was associated with increased body mass index (BMI) at 2-5 years of age in 297 mother-child pairs from Cincinnati, Ohio (HOME Study).

METHODS

Urinary BPA concentrations were measured in samples collected from pregnant women during the second and third trimesters and their children at 1 and 2 years of age. BMI z-scores were calculated from weight/height measures conducted annually from 2 through 5 years of age. We used linear mixed models to estimate BMI differences or trajectories with increasing creatinine-normalized BPA concentrations.

RESULTS

After confounder adjustment, each 10-fold increase in prenatal (ß = -0.1; 95% CI: -0.5, 0.3) or early-childhood (ß = -0.2; 95% CI: -0.6, 0.1) BPA concentrations was associated with a modest and nonsignificant reduction in child BMI. These inverse associations were suggestively stronger in girls than in boys [prenatal effect measure modification (EMM) p-value = 0.30, early-childhood EMM p-value = 0.05], but sex-specific associations were imprecise. Children in the highest early-childhood BPA tercile had lower BMI at 2 years (difference = -0.3; 95% CI: -0.6, 0.0) and larger increases in their BMI slope from 2 through 5 years (BMI increase per year = 0.12; 95% CI: 0.07, 0.18) than children in the lowest tercile (BMI increase per year = 0.07; 95% CI: 0.01, 0.13). All associations were attenuated without creatinine normalization.

CONCLUSIONS

Prenatal and early-childhood BPA exposures were not associated with increased BMI at 2-5 years of age, but higher early-childhood BPA exposures were associated with accelerated growth during this period.

Full text, graphs, charts and 40 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4216170/

“Growing evidence from research on laboratory animals, wildlife, and humans supports the view that **BPA produces an endocrine disrupting effect and adversely affects male reproductive function.**”

Reviews Of Environmental Contamination And Toxicology • December 2014

Adverse effects of bisphenol A on male reproductive function

Author information
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Abstract

BPA is a ubiquitous environmental contaminant, resulting mainly from manufacturing,use or disposal of plastics of which it is a component, and the degradation of industrial plastic-related wastes. Growing evidence from research on laboratory animals, wildlife, and humans supports the view that BPA produces an endocrine disrupting effect and adversely affects male reproductive function. To better understand the adverse effects caused by exposure to BPA, we performed an up-to-date literature review on the topic, with particular emphasis on in utero exposure, and associated effects on spermatogenesis, steroidogenesis, and accessory organs. BPA studies on experimental animals show that effects are generally more detrimental during in utero exposure, a critical developmental stage for the embryo. BPA has been found to produce several defects in the embryo, such as feminization of male fetuses, atrophy of the testes and epididymides, increased prostate size, shortening of AGD, disruption of BTB, and alteration of adult sperm parameters (e.g.,sperm count, motility, and density). BPA also affects embryo thyroid development. During the postnatal and pubertal periods and adulthood, BPA affects the hypothalamic-pituitary-testicular axis by modulating hormone (e.g., LH and FSH,androgen and estrogen) synthesis, expression and function of respective receptors(ER, AR). These effects alter sperm parameters. BPA also induces oxidative stress in the testis and epididymis, by inhibiting antioxidant enzymes and stimulating lipid peroxidation. This suggests that employing antioxidants may be a promising strategy to relieve BPA-induced disturbances. Epidemiological studies have also provided data indicating that BPA alters male reproductive function in humans. These investigations revealed that men occupationally exposed to BPA had high blood/urinary BPA levels, and abnormal semen parameters. BPA-exposed men also showed reduced libido and erectile ejaculatory difficulties; moreover, the overall BPA effects on male reproduction appear to be more harmful if exposure occurs in utero. The regulation of BPA and BPA-related products should be reinforced, particularly where exposure during the fetal period can occur. The current TDI for BPA is proposed as 25 and 50 1-1g/kg bwt/day (European Food Safety Authority and Health Canada, respectively). Based on the evidence available, we believe that a TDI value of 5 1-1g/kg bwt/day is more appropriate (the endpoint is modulation of rat testicular function). Certain BPA derivatives are being considered as alternatives to BPA. However, certain of these related products display adverse effects that are similar to those of BPA. These effects should be carefully considered before using them as final alternatives to BPA in plastic production.

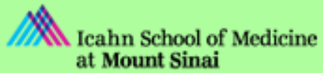
http://www.ncbi.nlm.nih.gov/pubmed/24162092

“These results suggest that prenatal exposure to BPA may be related to **increased behavior problems** in school age boys, but not girls.”

Neurotoxicology • December 2014

Prenatal bisphenol A exposure and maternally reported behavior in boys and girls

Author information



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Abstract

Prenatal exposure to gonadal hormones plays a major role in the normal development of the male and female brain and sexually dimorphic behaviors. Hormone-dependent differences in brain structure and function suggest that exposure to exogenous endocrine disrupting chemicals may be associated with sex-specific alterations in behavior. Bisphenol A (BPA) is an environmental chemical that has been shown to alter estrogen, androgen, and thyroid hormone signaling pathways. Epidemiological and experimental studies suggest associations between prenatal exposure to BPA and child behavior, however data are inconsistent, and few studies have examined school age children. We examined BPA concentration in spot urine samples from women at mean 27 weeks of pregnancy in relation to child behavior assessed at age 6-10 years using the parent-completed Child Behavior Checklist (CBCL). We report associations between maternal BPA urinary concentrations and several CBCL scores in 153 children (77 boys and 76 girls). We observed a significant interaction between maternal urinary BPA and sex for several behaviors (externalizing, aggression, Anxiety Disorder, Oppositional/Defiant Disorder and Conduct Disorder traits), but no significant associations between BPA and scores on any CBCL scales. However in analyses restricted to children of mothers with detectable prenatal urinary BPA (n=125), BPA was associated with moderately increased internalizing and externalizing behaviors, withdrawn/depressed behavior, somatic problems, and Oppositional/Defiant Disorder traits in boys. In addition we observed a significant interaction between BPA and sex for several behaviors (externalizing, withdrawn/depressed, rule-breaking, Oppositional/Defiant Disorder traits, and Conduct Disorder traits). These results suggest that prenatal exposure to BPA may be related to increased behavior problems in school age boys, but not girls.

Full text, PDF, charts, graphs and 69 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4362616/pdf/nihms-639682.pdf

CONCLUSIONS AND RELEVANCE:

“These results provide evidence suggesting that prenatal but not postnatal exposure to BPA is associated with diminished lung function and the development of persistent wheeze in children.”

The Journal Of The American Medical Association • Pediatrics • December 2014

Bisphenol a exposure and the development of wheeze and lung function in children through age 5 years

Author information

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Abstract

IMPORTANCE

Bisphenol A (BPA), a prevalent endocrine-disrupting chemical, has been associated with wheezing in children, but few studies have examined its effect on lung function or wheeze in older children.

OBJECTIVES

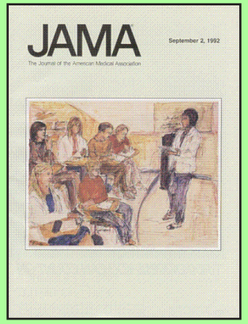
To test whether BPA exposure is associated with lung function, with wheeze, and with pattern of wheeze in children during their first 5 years.

DESIGN, SETTING, AND PARTICIPANTS

A birth cohort study, enrolled during early pregnancy in the greater Cincinnati, Ohio, area among 398 mother-infant dyads. We collected maternal urine samples during pregnancy (at 16 and 26 weeks) and child urine samples annually to assess gestational and child BPA exposure.

MAIN OUTCOMES AND MEASURES

We assessed parent-reported wheeze every 6 months for 5 years and measured child forced expiratory volume in the first second of expiration (FEV1) at age 4 and 5 years. We evaluated associations of BPA exposure with respiratory outcomes, including FEV1, child wheeze, and wheeze phenotype.



RESULTS

Urinary BPA concentrations and FEV1 data were available for 208 children and urinary BPA concentrations and parent-reported wheeze data were available for 360 children. The mean maternal urinary BPA concentration ranged from 0.53 to 293.55 μg/g of creatinine. In multivariable analysis, every 10-fold increase in the mean maternal urinary BPA concentration was associated with a 14.2% (95% CI, -24.5% to -3.9%) decrease in the percentage predicted FEV1 at 4 years, but no association was found at 5 years. In multivariable analysis, every 10-fold increase in the mean maternal urinary BPA concentration was marginally associated with a 54.8% increase in the odds of wheezing (adjusted odds ratio, 1.55; 95% CI, 0.91-2.63). While the mean maternal urinary BPA concentration was not associated with wheeze phenotype, a 10-fold increase in the 16-week maternal urinary BPA concentration was associated with a 4.27-fold increase in the odds of persistent wheeze (adjusted odds ratio, 4.27; 95% CI, 1.37-13.30). Child urinary BPA concentrations were not associated with FEV1 or wheeze.

Full text, graphs, charts and 47 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4535321/

“Environmental contaminants are known to exert endocrine-disrupting effects on the reproductive axis of animals. Many of these molecules can affect steroid biosynthesis or estrogen receptor signaling by behaving as estrogen-like molecules (“xenoestrogens”), or by exerting estrogenmodulatory effects. Exposure to some compounds has been correlated with the skewing of sex ratios in aquatic species, feminization and demasculinization of male animals, **declines in human sperm counts, and overall diminution in fertility of birds, fish, and mammals.**”

Current Trends In Endocrinology • December 2014

Familiar and novel reproductive endocrine disruptors: xenoestrogens, dioxins and nanoparticles

Abstract

Environmental contaminants are known to exert endocrine-disrupting effects on the reproductive axis of animals. Many of these molecules can affect steroid biosynthesis or estrogen-receptor signaling by behaving as estrogen-like molecules (“xenoestrogens”), or by exerting estrogenmodulatory effects. Exposure to some compounds has been correlated with the skewing of sex ratios in aquatic species, feminization and demasculinization of male animals, declines in human sperm counts, and overall diminution in fertility of birds, fish, and mammals. We herein devote space to several classes of endocrine-disrupting compounds (EDCs), including estrogenic substances such as bisphenol A (BPA), molecules that can behave at times anti-estrogenically while activating the aromatic hydrocarbon receptor (AHR), such as dioxins (a known human carcinogen), and novel, ubiquitous molecules such as nanoparticles, particularly gold nanoparticles (GNPs), that appear to alter the sex-steroid biosynthetic pathway.

Full text, graphs, charts and 114 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364387/

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“Observations demonstrate that a mixture of plastic derived compounds, BPA and phthalates, **can promote epigenetic transgenerational inheritance of adult onset disease**. The sperm DMR provide potential epigenetic biomarkers for transgenerational disease and/or ancestral environmental exposures.”

PLoS One • January 2013

Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations

Author information

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Abstract

Environmental compounds are known to promote epigenetic transgenerational inheritance of adult onset disease in subsequent generations (F1-F3) following ancestral exposure during fetal gonadal sex determination. The current study was designed to determine if a mixture of plastic derived endocrine disruptor compounds bisphenol-A (BPA), bis(2-ethylhexyl)phthalate (DEHP) and dibutyl phthalate (DBP) at two different doses promoted epigenetic transgenerational inheritance of adult onset disease and associated DNA methylation epimutations in sperm. Gestating F0 generation females were exposed to either the “plastics” or “lower dose plastics” mixture during embryonic days 8 to 14 of gonadal sex determination and the incidence of adult onset disease was evaluated in F1 and F3 generation rats. There were significant increases in the incidence of total disease/abnormalities in F1 and F3 generation male and female animals from plastics lineages. Pubertal abnormalities, testis disease, obesity, and ovarian disease (primary ovarian insufficiency and polycystic ovaries) were increased in the F3 generation animals. Kidney and prostate disease were only observed in the direct fetally exposed F1 generation plastic lineage animals. Analysis of the plastics lineage F3 generation sperm epigenome previously identified 197 differential DNA methylation regions (DMR) in gene promoters, termed epimutations. A number of these transgenerational DMR form a unique direct connection gene network and have previously been shown to correlate with the pathologies identified. Observations demonstrate that a mixture of plastic derived compounds, BPA and phthalates, can promote epigenetic transgenerational inheritance of adult onset disease. The sperm DMR provide potential epigenetic biomarkers for transgenerational disease and/or ancestral environmental exposures.

Full text, graphs, charts and 125 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3554682/

“We identified a **race/ethnicity-specific association** of phthalates with childhood obesity in a nationally representative sample.”

Environmental Health Perspectives • April 2013

Race/ethnicity-specific associations of urinary phthalates with childhood body mass in a nationally representative sample

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BACKGROUND

Phthalates have antiandrogenic effects and may disrupt lipid and carbohydrate metabolism. Racial/ethnic subpopulations have been documented to have varying urinary phthalate concentrations and prevalences of childhood obesity.

OBJECTIVE

We examined associations between urinary phthalate metabolites and body mass outcomes in a nationally representative sample of U.S. children and adolescents.

METHODS

We performed stratified and whole-sample cross-sectional analyses of 2,884 children 6-19 years of age who participated in the 2003-2008 National Health and Nutrition Examination Survey. Multivariable linear and logistic analyses of body mass index z-score, overweight, and obesity were performed against molar concentrations of low-molecular-weight (LMW), high-molecular-weight (HMW), and di-2-ethylhexylphthalate (DEHP) metabolites, controlling for sex, television watching, caregiver education, caloric intake, poverty-income ratio, race/ethnicity, serum cotinine, and age group. We used sensitivity analysis to examine robustness of results to removing sample weighting, normalizing phthalate concentrations for molecular weight, and examining different dietary intake covariates.

RESULTS

In stratified, multivariable models, each log unit (roughly 3-fold) increase in LMW metabolites was associated with 21% and 22% increases in odds (95% CI: 1.05-1.39 and 1.07-1.39, respectively) of overweight and obesity, and a 0.090-SD unit increase in BMI z-score (95% CI: 0.003-0.18), among non-Hispanic blacks. Significant associations were not identified in any other racial/ethnic subgroup or in the study sample as a whole after controlling for potential confounders, associations were not significant for HMW or DEHP metabolites, and results did not change substantially with sensitivity analysis.

CONCLUSIONS

We identified a race/ethnicity-specific association of phthalates with childhood obesity in a nationally representative sample. Further study is needed to corroborate the association and evaluate genetic/epigenomic predisposition and/or increased phthalate exposure as possible explanations for differences among racial/ethnic subgroups.

Full text, graphs, charts and 51 references:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3620751/

“In model organisms, **BPA exposure is linked to metabolic disorders, infertility, cancer, and behavior anomalies**. Recently, BPA exposure has been linked to DNA methylation changes, indicating that epigenetic mechanisms may be relevant. We investigated effects of exposure on genomic imprinting in the mouse as imprinted genes are regulated by differential DNA methylation and aberrant imprinting **disrupts fetal, placental, and postnatal development**.”

Plus One Genetics • April 2013

Bisphenol A Exposure Disrupts Genomic Imprinting in the Mouse

By Martha Susiarjo, Isaac Sasson, Clementina Mesaros and Marisa S. Bartolomei

Abstract

Exposure to endocrine disruptors is associated with developmental defects. One compound of concern, to which humans are widely exposed, is bisphenol A (BPA). In model organisms, BPA exposure is linked to metabolic disorders, infertility, cancer, and behavior anomalies. Recently, BPA exposure has been linked to DNA methylation changes, indicating that epigenetic mechanisms may be relevant. We investigated effects of exposure on genomic imprinting in the mouse as imprinted genes are regulated by differential DNA methylation and aberrant imprinting disrupts fetal, placental, and postnatal development. Through allele-specific and quantitative real-time PCR analysis, we demonstrated that maternal BPA exposure during late stages of oocyte development and early stages of embryonic development significantly disrupted imprinted gene expression in embryonic day (E) 9.5 and 12.5 embryos and placentas. The affected genes included Snrpn, Ube3a, Igf2, Kcnq1ot1, Cdkn1c, and Ascl2; mutations and aberrant regulation of these genes are associated with imprinting disorders in humans. Furthermore, the majority of affected genes were expressed abnormally in the placenta. DNA methylation studies showed that BPA exposure significantly altered the methylation levels of differentially methylated regions (DMRs) including the Snrpn imprinting control region (ICR) and Igf2 DMR1. Moreover, exposure significantly reduced genome-wide methylation levels in the placenta, but not the embryo. Histological and immunohistochemical examinations revealed that these epigenetic defects were associated with abnormal placental development. In contrast to this early exposure paradigm, exposure outside of the epigenetic reprogramming window did not cause significant imprinting perturbations. Our data suggest that early exposure to common environmental compounds has the potential to disrupt fetal and postnatal health through epigenetic changes in the embryo and abnormal development of the placenta.

Author Summary

BPA is a widely used compound to which humans are exposed, and recent studies have demonstrated the association between exposure and adverse developmental outcomes in both animal models and humans. Unfortunately, exact mechanisms of BPA–induced health abnormalities are unclear, and elucidation of these relevant biological pathways is critical for understanding the public health implication of exposure. Recently, increasing data have demonstrated the ability of BPA to induce changes in DNA methylation, suggesting that epigenetic mechanisms are relevant. In this work, we study effects of BPA exposure on expression and regulation of imprinted genes in the mouse. Imprinted genes are regulated by differential DNA methylation, and they play critical roles during fetal, placental, and postnatal development. We have found that fetal exposure to BPA at physiologically relevant doses alters expression and methylation status of imprinted genes in the mouse embryo and placenta, with the latter tissue exhibiting the more significant changes. Additionally, abnormal imprinting is associated with defective placental development. Our data demonstrate that BPA exposure may perturb fetal and postnatal health through epigenetic changes in the embryo as well as through alterations in placental development.

Full text, graphs, charts and 75 references

http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1003401

“Overall, we demonstrate that **low-dose prenatal BPA exposure induces lasting epigenetic disruption in the brain** that possibly underlie enduring effects of BPA on brain function and behavior, especially regarding sexually dimorphic phenotypes.”

Proceedings Of The National Academy Of Science USA • June 2013

Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure

Author information

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Abstract

Bisphenol A (BPA) is an estrogenic endocrine disruptor widely used in the production of plastics. Increasing evidence indicates that in utero BPA exposure affects sexual differentiation and behavior; however, the mechanisms underlying these effects are unknown. We hypothesized that BPA may disrupt epigenetic programming of gene expression in the brain. Here, we provide evidence that maternal exposure during pregnancy to environmentally relevant doses of BPA (2, 20, and 200 µg/kg/d) in mice induces sex-specific, dose-dependent (linear and curvilinear), and brain region-specific changes in expression of genes encoding estrogen receptors (ERs; ERa and ERß) and estrogen-related receptor-y in juvenile offspring. Concomitantly, BPA altered mRNA levels of epigenetic regulators DNA methyltransferase (DNMT) 1 and DNMT3A in the juvenile cortex and hypothalamus, paralleling changes in estrogen-related receptors. Importantly, changes in ERa and DNMT expression in the cortex (males) and hypothalamus (females) were associated with DNA methylation changes in the ERa gene. BPA exposure induced persistent, largely sex-specific effects on social and anxiety-like behavior, leading to disruption of sexually dimorphic behaviors. Although postnatal maternal care was altered in mothers treated with BPA during pregnancy, the effects of in utero BPA were not found to be mediated by maternal care. However, our data suggest that increased maternal care may partially attenuate the effects of in utero BPA on DNA methylation. Overall, we demonstrate that low-dose prenatal BPA exposure induces lasting epigenetic disruption in the brain that possibly underlie enduring effects of BPA on brain function and behavior, especially regarding sexually dimorphic phenotypes.

Full text, graphs, charts and 51 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3683772/

“Bisphenol A (BPA), a chemical used in many consumer products, **interferes with the endocrine system of mammals, including humans** ... both the quality and quantity of spermatozoa were decreased ... exposure of male mice to BPA resulted in abnormal offspring that were smaller with a low-quality pelage when they were 35 days old. In conclusion, **BPA hampers spermatogenesis and the subsequent development of offspring**.”

Reproduction, Fertility And Development • October 2013

Exposure to bisphenol A results in a decline in mouse spermatogenesis

Author information

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Abstract

Bisphenol A (BPA), a chemical used in many consumer products, interferes with the endocrine system of mammals, including humans. The aim of the present study was to investigate the effect of BPA on spermatogenesis and semen quality. The objective of this study was to assess the effects of BPA on mouse spermatogenesis. CD1 mice were used in all experiments. Mice were treated with different doses of BPA (0, 20 and 40 μg kg^{-1} day^{-1} from postnatal Day (PND) 3 to PND21, PND 35 or PND49. After 5 weeks BPA treatment, oestrogen receptor alpha expression was increased in mouse testis, whereas the meiotic progression of germ cells was slowed. Thus, both the quality and quantity of spermatozoa were decreased in 7-week-old mice. However, BPA had no effect on DNA methylation of imprinted genes such as Igf2, Igf2r, Peg3 and H19, in germ cells. In addition, exposure of male mice to BPA resulted in abnormal offspring that were smaller with a low-quality pelage when they were 35 days old. In conclusion, BPA hampers spermatogenesis and the subsequent development of offspring.

http://www.ncbi.nlm.nih.gov/pubmed/22951085

“The exposure of BPA to humans occurs through food contamination from polycarbonate bottles and food and beverage cans. Dust is also a contributor to the total daily exposure of BPA. Thus, BPA has a high potential for human consumption. **BPA is toxic to aquatic organisms, animals and humans. BPA is cytotoxic and mutagenic** and exerts various adverse effects on immune, endocrine, reproductive, developmental and nervous systems in animals and human and **exhibits toxicity by all routes of exposure**. **Metabolism of BPA is much more rapid in humans** than in rodents.”

Current Molecular Pharmacology • November 2013

Nephrotoxicity of bisphenol A (BPA): an updated review

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Abstract

Bisphenol A (BPA), the highest volume chemical produced in the whole world is widely used in the production of polycarbonate plastics and epoxy resins. Polycarbonate plastics are used especially in the manufacture of consumer products. The exposure of BPA to humans occurs through food contamination from polycarbonate bottles and food and beverage cans. Dust is also a contributor to the total daily exposure of BPA. Thus, BPA has a high potential for human consumption. The U.S. Food and Drug Administration (FDA) recently announced concern about the safety of BPA and the need for more research data. This article reviews toxicity of BPA in general and kidney in particular using clinical and experimental literature. BPA is toxic to aquatic organisms, animals and humans. BPA is cytotoxic and mutagenic and exerts various adverse effects on immune, endocrine, reproductive, developmental and nervous systems in animals and human and exhibits toxicity by all routes of exposure. Metabolism of BPA is much more rapid in humans than in rodents. BPA increases estrogen metabolism in the kidney and upregulates cytochrome p-450 aromatase activity by means of steroidogenesis. BPA acts as biomarker for renal disease and exhibits nephrotoxicity. BPA toxicity with reference to human exposure level and also carcinogenicity are lacking. While focusing on kidney, this review suggests that further research is required to evaluate the molecular mechanism of BPA induced nephrotoxicity. Protective role of antioxidants against BPA induced toxicity / nephrotoxicity is discussed in this literature.

http://www.ncbi.nlm.nih.gov/pubmed/24720537

“A comprehensive literature search found **91 studies linking bisphenol A to human health; 53 published within the last year**. This review outlines this body of literature, showing associations between BPA exposure and adverse perinatal, childhood, and adult health outcomes, including reproductive and developmental effects, metabolic disease, and other health effects.”

Reproductive Toxicology • December 2013

Bisphenol A and human health: a review of the literature

Author information

By J. R. Rochester

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Abstract

There is growing evidence that bisphenol A (BPA) may adversely affect humans. BPA is an endocrine disruptor that has been shown to be harmful in laboratory animal studies. Until recently, there were relatively few epidemiological studies examining the relationship between BPA and health effects in humans. However, in the last year, the number of these studies has more than doubled. A comprehensive literature search found 91 studies linking BPA to human health; 53 published within the last year. This review outlines this body of literature, showing associations between BPA exposure and adverse perinatal, childhood, and adult health outcomes, including reproductive and developmental effects, metabolic disease, and other health effects. These studies encompass both prenatal and postnatal exposures, and include several study designs and population types. While it is difficult to make causal links with epidemiological studies, the growing human literature correlating environmental BPA exposure to adverse effects in humans, along with laboratory studies in many species including primates, provides increasing support that environmental BPA exposure can be harmful to humans, especially in regards to behavioral and other effects in children.

http://www.ncbi.nlm.nih.gov/pubmed/23994667

“These results suggest that prenatal exposure to **BPA may affect child behavior**, and differently among boys and girls.”

Environmental Health Perspectives • August 2012

Prenatal bisphenol a exposure and child behavior in an inner-city cohort

Author information

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Abstract

BACKGROUND

Experimental laboratory evidence suggests that bisphenol A (BPA), an endocrine disruptor, is a neurodevelopmental toxicant. However, there have been limited and inconclusive results with respect to sex-specific BPA effects on child behavior.

OBJECTIVE

We examined the association between prenatal BPA exposure and child behavior, adjusting for postnatal BPA exposure and hypothesizing sex-specific effects.

METHODS

We followed African-American and Dominican women and their children from pregnancy to child’s age 5 years, collecting spot urine samples from the mothers during pregnancy (34 weeks on average) and from children between 3 and 4 years of age to estimate BPA exposure. We assessed child behavior between 3 and 5 years of age using the Child Behavior Checklist (CBCL) and used generalized linear models to test the association between BPA exposure and child behavior, adjusting for potential confounders.

RESULTS

The analysis was conducted on 198 children (87 boys and 111 girls). Among boys, high prenatal BPA exposure (highest quartile vs. the lowest three quartiles) was associated with significantly higher CBCL scores (more problems) on Emotionally Reactive [1.62 times greater; 95% confidence interval (CI): 1.13, 2.32] and Aggressive Behavior syndromes (1.29 times greater; 95% CI: 1.09, 1.53). Among girls, higher exposure was associated with lower scores on all syndromes, reaching statistical significance for Anxious/Depressed (0.75 times as high; 95% CI: 0.57, 0.99) and Aggressive Behavior (0.82 times as high; 95% CI: 0.70, 0.97).

CONCLUSION

These results suggest that prenatal exposure to BPA may affect child behavior, and differently among boys and girls.

Full text, graphs, charts and 43 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3440080/

Neuropathology • August 2012

Bisphenol A, an endocrine-disrupting chemical, and brain development

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Abstract

“Bisphenol A (BPA) is an endocrine-disrupting chemical, widely used in various industries and the field of dentistry. The consequent increase in BPA exposure among humans has led us to some concerns regarding the potential deleterious effects on reproduction and brain development. **The emphasis of this review is on the effects of prenatal and lactational exposure to low doses of BPA on brain development in mice.** We demonstrated that prenatal exposure to BPA affected fetal murine neocortical development by accelerating neuronal differentiation/migration during the early embryonic stage, which was associated with up- and down-regulation of the genes critical for brain development, including the basic helix-loop-helix transcription factors. In the adult mice brains, both abnormal neocortical architecture and abnormal corticothalamic projections persisted in the group exposed to the BPA. Functionally, BPA exposure disturbed murine behavior, accompanied with a disrupted neurotransmitter system, including monoamines, in the postnatal development period and in adult mice. We also demonstrated that epigenetic alterations in promoter-associated CpG islands might underlie some of the effects on brain development after exposure to BPA.”

http://www.ncbi.nlm.nih.gov/pubmed/22239237

“The estimated median daily intake (EDI) of 8 Bisphenols through dust ingestion in the U.S., China, Japan, and Korea was 12.6, 4.61, 15.8, and 18.6 ng/kg body weight (bw)/day, respectively, for toddlers and 1.72, 0.78, 2.65, and 3.13 ng/kg bw/day, respectively, for adults. **This is the first report on the occurrence of bisphenols, other than BPA, in indoor dust.**”

Environmental Science & Technology • August 2012

Occurrence of eight bisphenol analogues in indoor dust from the United States and several Asian countries: implications for human exposure

Author information

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Abstract

Bisphenol A has been reported to be a ubiquitous contaminant in indoor dust, and human exposure to this compound is well documented. Information on the occurrence of and human exposure to other bisphenol analogues is limited. In this study, eight bisphenol analogues, namely 2,2-bis(4-hydroxyphenyl)propane (BPA), 4,4’-(hexafluoroisopropylidene)diphenol (BPAF), 4,4’-(1-phenylethylidene)bisphenol (BPAP), 2,2-bis(4-hydroxyphenyl)butane (BPB), 4,4’-dihydroxydiphenylmethane (BPF), 4,4’-(1,4-phenylenediisopropylidene)bisphenol (BPP), 4,4’- sulfonyldiphenol (BPS), and 4,4’-cyclohexylidenebisphenol (BPZ), were determined in indoor dust samples (n = 156) collected from the United States (U.S.), China, Japan, and Korea. Samples were extracted by solid-liquid extraction, purified by automated solid phase extraction methods, and determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The total concentrations of bisphenols (∑BPs; sum of eight bisphenols) in dust were in the range of 0.026-111 μg/g (geometric mean: 2.29 μg/g). BPA, BPS, and BPF were the three major bisphenols, accounting for >98% of the total concentrations. Other bisphenol analogues were rare or not detected, with the exception of BPAF, which was found in 76% of the 41 samples collected in Korea (geometric mean: 0.0039 μg/g). The indoor dust samples from Korea contained the highest concentrations of both individual and total bisphenols. BPA concentrations in dust were compared among three microenvironments (house, office, and laboratory). The estimated median daily intake (EDI) of ∑BPs through dust ingestion in the U.S., China, Japan, and Korea was 12.6, 4.61, 15.8, and 18.6 ng/kg body weight (bw)/day, respectively, for toddlers and 1.72, 0.78, 2.65, and 3.13 ng/kg bw/day, respectively, for adults. This is the first report on the occurrence of bisphenols, other than BPA, in indoor dust.

http://www.ncbi.nlm.nih.gov/pubmed/22784190

“Urinary BPA concentration was significantly associated with **obesity** ...”

JAMA • September 2012

Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents

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Abstract

CONTEXT

Bisphenol A (BPA), a manufactured chemical, is found in canned food, polycarbonate-bottled liquids, and other consumer products. In adults, elevated urinary BPA concentrations are associated with obesity and incident coronary artery disease. BPA exposure is plausibly linked to childhood obesity, but evidence is lacking to date.

OBJECTIVE

To examine associations between urinary BPA concentration and body mass outcomes in children.

DESIGN, SETTING, AND PARTICIPANTS

Cross-sectional analysis of a nationally representative subsample of 2838 participants aged 6 through 19 years randomly selected for measurement of urinary BPA concentration in the 2003-2008 National Health and Nutrition Examination Surveys.

MAIN OUTCOME MEASURES

Body mass index (BMI), converted to sex- and age-standardized z scores and used to classify participants as overweight (BMI ≥85th percentile for age/sex) or obese (BMI ≥95th percentile).

RESULTS

Median urinary BPA concentration was 2.8 ng/mL (interquartile range, 1.5-5.6). Of the participants, 1047 (34.1% [SE, 1.5%]) were overweight and 590 (17.8% [SE, 1.3%]) were obese. Controlling for race/ethnicity, age, caregiver education, poverty to income ratio, sex, serum cotinine level, caloric intake, television watching, and urinary creatinine level, children in the lowest urinary BPA quartile had a lower estimated prevalence of obesity (10.3% [95% CI, 7.5%-13.1%]) than those in quartiles 2 (20.1% [95% CI, 14.5%-25.6%]), 3 (19.0% [95% CI, 13.7%-24.2%]), and 4 (22.3% [95% CI, 16.6%-27.9%]). Similar patterns of association were found in multivariable analyses examining the association between quartiled urinary BPA concentration and BMI z score and in analyses that examined the logarithm of urinary BPA concentration and the prevalence of obesity. Obesity was not associated with exposure to other environmental phenols commonly used in other consumer products, such as sunscreens and soaps. In stratified analysis, significant associations between urinary BPA concentrations and obesity were found among whites ($P < .001$) but not among blacks or Hispanics.

CONCLUSIONS

Urinary BPA concentration was significantly associated with obesity in this cross-sectional study of children and adolescents. Explanations of the association cannot rule out the possibility that obese children ingest food with higher BPA content or have greater adipose stores of BPA.

http://www.ncbi.nlm.nih.gov/pubmed/22990270

“Multiple linear regression analyses showed that urine BPA concentrations were significantly associated with increasing BMI values in all subjects after adjustment for age and sex and the results were similar before and after corrected by urine specific gravity. There is a possibility that **BPA exposure increases Body Mass Index in school children.**”

Environmental Health • October 2012

Association between bisphenol A exposure and body mass index in Chinese school children: a cross-sectional study

Author information
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Abstract

BACKGROUND

There is increasing evidence suggesting that Bisphenol A (BPA), one of the highest volume chemicals produced worldwide, can interfere with the body’s natural weight control mechanisms to promote obesity. However, epidemiological studies for this are limited, especially for children.

METHODS

A cross-sectional study was conducted to investigate the association between BPA exposure and body mass index (BMI) in school children. Three primary and three middle schools were randomly selected from 26 primary and 30 middle candidate schools in Changning District of Shanghai City in China. According to the BMI-based criteria by age and sex for screening of overweight or obese children, we randomly chose 20 obese, 10 overweight, and 30 normal weight children aged 8-15 years of age from each selected school. First morning urine was collected and total urine BPA concentrations were determined by ultra-performance liquid chromatography tandem mass spectrometry. Multiple linear regression analysis was conducted to examine the association of urine BPA concentrations and daily intake estimates with BMI.

RESULTS

BPA was detected in 84.9% of urine samples with a geometric mean of 0.45 ng/mL. The daily intake estimates ranged from 0.03 μg/day to 1.96 μg/day with a geometric mean of 0.37 μg/day. The average urine BPA concentrations and daily intake estimates were similar for boys and girls, but significantly higher in older children than younger ones, and showed an increasing trend with BMI. Multiple linear regression analyses showed that urine BPA concentrations were significantly associated with increasing BMI values in all subjects after adjustment for age and sex and the results were similar before and after corrected by urine specific gravity. When stratified by age or sex, the associations remained significant in females and in those 8-11 years of age before corrected by specific gravity. Similar results were shown for the association between BMI and daily intake estimates.

CONCLUSIONS

There is a possibility that BPA exposure increases BMI in school children. Given the cross-sectional nature of this study, longitudinal studies are warranted to confirm BPA exposure as a contributor to increased BMI in children.

Full text, graphs, charts and 52 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3549797/

SCHOOL LUNCH PROGRAMS IN THE USA

A professor of sociology at New York’s Hunter College, Janet Poppendieck, discovered that it’s not hard to find people with negative memories of their school lunches. As part of her work she asked students at various universities and colleges to recount their experiences and many of the responses weren’t exactly nostalgic: “*I would dread the fact that I needed to eat that food*”; “*High school lunch was gross*,” or, more succinctly, “*Greasy! Fatty! Pricey!*”

The National School Lunch Program, created to provide subsidized meals to the country’s impoverished schoolchildren, serves 31 million meals on an average day, but as Poppendieck details in “Free for All: Fixing School Food in America,” her new book about the country’s school cafeterias, many of them are un-nutritious, uninspiring and tasteless. The most popular meal: pepperoni pizza, nachos, a peanut butter cookie and diet soda — with a whopping 1,116 calories and 51 grams of fat.

How did America’s school lunches get so bad? Budget restrictions while trillions are spent on wars and foreign aid, in-school competition from giant multinationals producing cheap, low-quality food, and arcane federal guidelines—calorie minimums mixed with fat-content maximums and more—along with a complicated three-tiered payment system based on a child’s poverty and the stigmas associated with subsidized food. The drugs we eat in our food create unexpected challenges for even the most well meaning parents and these are all various components of failed responsibility for the depressing state of the American school cafeteria. Removing drugs from school cafeterias should be a social imperative or we’ll lose generations to mutagens, carcinogens and neurotoxins.

“Bisphenol A (BPA), a toxic chemical released from plastics, **produces respiratory arrest and hypotension after a latency** ... The present results indicate that BPA attenuates the protective cardio-respiratory reflexes ...”

Neuroscience Letters • November 2012

Bisphenol A attenuates phenylbiguanide-induced cardio-respiratory reflexes in anaesthetized rats

Author information

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Abstract

Bisphenol A (BPA), a toxic chemical released from plastics, produces respiratory arrest and hypotension after a latency. The latency was similar to the reflex apnoea induced by the vagal C fibre stimulation. Therefore, the present study was undertaken to examine the effects of chronic and acute exposure to BPA on cardio-respiratory reflexes elicited by phenylbiguanide (PBG). Acute and chronic experiments were performed on adult female rats. In chronic experiments, the animals were ingested with pellets containing BPA (2 µg/kg body weight) or without BPA (time-matched control) for 30 days. Subsequently, the animals were anaesthetized and prepared for recording blood pressure, ECG and respiratory excursions. PBG was injected through jugular vein to evoke reflexes in these animals. In acute experiments, the PBG reflexes were obtained before and after injecting BPA/ethanol. Also vagal afferent activity was recorded in some rats. In time-matched control rats, PBG produced bradycardia, hypotension and tachypnoea over a period of time. The maximal changes were around 50-65%. In BPA treated group, the PBG-induced heart rate and respiratory frequency changes were attenuated significantly. Acute exposure of animals to BPA (35 mg/kg body weight) for 30 min also attenuated the PBG-induced responses significantly. The attenuation of the PBG reflex responses by BPA in acute experiments was associated with decreased vagal afferent activity. The present results indicate that BPA attenuates the protective cardio-respiratory reflexes due to decreased vagal afferent activity.

http://www.ncbi.nlm.nih.gov/pubmed/23041044

Human Reproduction • December 2012

Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF

Author information

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Ye X, Calafat AM, Petrozza JC, Wright D, Hauser R.

Abstract

STUDY QUESTION

In women undergoing IVF, are urinary bisphenol A (BPA) concentrations associated with ovarian response and early reproductive outcomes, including oocyte maturation and fertilization, Day 3 embryo quality and blastocyst formation?

SUMMARY ANSWER

Higher urinary BPA concentrations were found to be associated with decreased ovarian response, number of fertilized oocytes and decreased blastocyst formation.

WHAT IS KNOWN ALREADY

Experimental animal and in vitro studies have reported associations between BPA exposure and adverse reproductive outcomes. We previously reported an association between urinary BPA and decreased ovarian response [peak serum estradiol (E(2)) and oocyte count at the time of retrieval] in women undergoing IVF; however, there are limited human data on reproductive health outcomes, such as fertilization and embryo development.

STUDY DESIGN, SIZE AND DURATION

Prospective preconception cohort study. One hundred and seventy-four women aged 18-45 years and undergoing 237 IVF cycles were recruited at the Massachusetts General Hospital Fertility Center, Boston, MA, USA, between November 2004 and August 2010. These women were followed until they either had a live birth or discontinued treatment. Cryothaw and donor egg cycles were not included in the analysis.

PARTICIPANTS/MATERIALS, SETTING AND METHODS

Urinary BPA concentrations were measured by online solid-phase extraction-high-performance liquid chromatography-isotope dilution-tandem mass spectrometry. Mixed effect models, poisson regression and multivariate logistic regression models were used wherever appropriate to evaluate the association between cycle-specific urinary BPA concentrations and measures of ovarian response, oocyte maturation (metaphase II), fertilization, embryo quality and cleavage rate. We accounted for correlation among multiple IVF cycles in the same woman using generalized estimating equations.

MAIN RESULTS AND THE ROLE OF CHANCE

The geometric mean (SD) for urinary BPA concentrations was 1.50 (2.22) µg/l. After adjustment for age and other potential confounders (Day 3 serum FSH, smoking, BMI), there was a significant linear dose-response association between increased urinary BPA concentrations and decreased number of oocytes (overall and mature), decreased number of normally fertilized oocytes and decreased E(2) levels (mean decreases of 40, 253 and 471 pg/ml for urinary BPA quartiles 2, 3 and 4, when compared with the lowest quartile, respectively; P-value for trend = 0.001). The mean number of oocytes and normally fertilized oocytes decreased by 24 and 27%, respectively, for the highest versus the lowest quartile of urinary BPA (trend test $P < 0.001$ and 0.002, respectively). Women with urinary BPA above the lowest quartile had decreased blastocyst formation (trend test P-value = 0.08).

LIMITATIONS AND REASONS FOR CAUTION

Potential limitations include exposure misclassification due to the very short half-life of BPA and its high variability over time; uncertainty about the generalizability of the results to the general population of women conceiving naturally and limited sample.

WIDER IMPLICATIONS OF THE FINDINGS

The results from this extended study, using IVF as a model to study early reproductive health outcomes in humans, indicate a negative dose-response association between urinary BPA concentrations and serum peak E(2) and oocyte yield, confirming our previous findings. In addition, we found significantly decreased metaphase II oocyte count and number of normally fertilizing oocytes and a suggestive association between BPA urinary concentrations and decreased blastocyst formation, thus indicating that BPA may alter reproductive function in susceptible women undergoing IVF.

STUDY FUNDING/COMPETING INTEREST(S)

This work was supported by grants ES009718 and ES000002 from the National Institute of Environmental Health Sciences and grant OH008578 from the National Institute for Occupational Safety and Health. None of the authors has actual or potential competing financial interests.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Full text, graphs, charts and 53 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501244/

“BPA is a weak estrogen agonist and its effects reported on animal studies are difficult to reconcile with mechanistic action of estrogen.”

Reproductive Toxicology • May 2011

Effect of perinatal and postnatal bisphenol A exposure to the regulatory circuits at the hypothalamus-pituitary-gonadal axis of CD-1 mice

Author information

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Abstract

Bisphenol A (BPA) is used in the manufacture of many products and is ubiquitous in the environment. Adverse effects of BPA on animal reproductive health have been reported, however most of the studies relied on the approaches in the assessment of conventional histology and anatomical features. The mechanistic actions of BPA are not clear. In the present study, a murine model was used to study potential effects of BPA exposure during perinatal and postnatal periods on endocrine functions of hypothalamic-pituitary-gonadal (HPG)-axis. At the hypothalamic-pituitary level, BPA exposure resulted in the up-regulation of the expression levels of KiSS-1, GnRH and FSH mRNA in both male and female pups. At the gonadal levels, BPA caused inhibition in the expressions of testicular steroidogenic enzymes and the synthesis of testosterone in the male pups. Conversely exposure to BPA resulted in a greater aromatase expression level and the synthesis of estrogen in the female pups. BPA is a weak estrogen agonist and its effects reported on animal studies are difficult to reconcile with mechanistic action of estrogen. In this study we hypothesized that the effects of BPA on reproductive dysfunction may be due to its actions on gonadal steroidogenesis and so the anomalous releases of endogenous steroid hormones. This non-ER-mediated effect is more potent in affecting the feedback regulatory circuits in the HPG-axis.

http://www.ncbi.nlm.nih.gov/pubmed/21182934

“Perinatal exposure to a low dose of BPA could increase sweet preference of male rats. **Calorie intake may be programmed during early life**, leading to changes of body weight depending on the gender.”

Neurotoxicology And Teratology • July 2011

Changed preference for sweet taste in adulthood induced by perinatal exposure to bisphenol A: A probable link to overweight and obesity

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Abstract

BACKGROUND

The preference of obesity has risen dramatically worldwide over the past decades. Some latest reports showed significant increase of obesity in men compared to women. Implication of environmental endocrine disruptors has been focused more and more. Numerous studies in vitro and vivo implied metabolic actions of bisphenol A (BPA), however much less consideration is given to the possibility of BPA exposure-induced change in gender-specific behaviors which result in obesity and overweight.

OBJECTIVES

To examine whether perinatal exposure to BPA at relative dose to environmental levels can influence sweet preference of male and female rats and consequently lead to alteration in bodyweight.

METHODS

Rats perinatally exposed to BPA at doses of 0.01, 0.1 and 1.0 mg/L were tested sweet preference for 0.25%, 0.5% saccharin and 15% sucrose by two-bottle choice (water vs. saccharin/sucrose). The food intake, liquid consumption and bodyweight of each rat were monitored daily. At the end of the test, the fat percentage and tail blood pressure were measured.

RESULTS

Significant sex difference of preference for 0.25% and 0.5% saccharin was shown in control and all BPA-treated groups ($p < 0.001$, female vs. male). 0.1 and 1.0 mg/L BPA treatment induced the increase of preference for 0.25% saccharin solution in males, but not in females. 0.1 mg/L BPA treatment increased sucrose preference in males at postnatal day (PND) 70 and 140 ($p < 0.05$ and $p < 0.001$, compared to control respectively) but decreased sucrose preference in females at PND 140 ($p < 0.05$, compared to control). The males treated by BPA showed overweight ($p < 0.001$), high fat percentage ($p < 0.001$) and tail blood pressure ($p < 0.05$) than control at PND 140.

CONCLUSION

Perinatal exposure to a low dose of BPA could increase sweet preference of male rats. Calorie intake may be programmed during early life, leading to changes of body weight depending on the gender. Although further researches concerning the mechanism are required, the results of the present study are particularly important with regards to the more significant increasing prevalence of obesity in men and the environmental endocrine disruptors.

http://www.ncbi.nlm.nih.gov/pubmed/21704699

“Higher BPA exposure is **associated with general and central obesity in the general adult population** of the United States ... longitudinal studies are needed to clarify the direction of the association.”

Environmental Research • August 2011

Urinary bisphenol A and obesity: NHANES 2003-2006

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Abstract

BACKGROUND

Bisphenol A (BPA) is a chemical suspected of causing endocrine and metabolic disruption in animals and humans. In rodents, in utero exposure to low-dose BPA is associated with weight gain. Detectable levels of BPA are found in most Americans due to its widespread use in the manufacture of food and drink packaging. We hypothesized that urinary BPA concentrations would be positively associated with general and central obesity.

METHODS

Cross-sectional analysis of urinary BPA concentrations, body mass index, and waist circumference in 2747 adults (aged 18-74), using pooled data from the 2003/04 and 2005/06 National Health and Nutrition Examination Surveys.

RESULTS

The creatinine-adjusted geometric mean urinary BPA concentration was 2.05µg/g creatinine (25th percentile: 1.18, 75% percentile: 3.33). Relative to those in the lowest BPA quartile, participants in the upper BPA quartiles were more likely to be classified as obese (quartile 2 odds ratio (OR): 1.85, 95% confidence interval (CI): 1.22, 2.79; quartile 3 OR: 1.60, 95% CI: 1.05-2.44; quartile 4 OR: 1.76, 95% CI: 1.06-2.94). Higher BPA concentration was also associated with abdominal obesity (quartile 2 OR: 1.62, 95% CI: 1.11, 2.36; quartile 3 OR: 1.39, 95% CI: 1.02-1.90; quartile 4 OR: 1.58, 95% CI: 1.03-2.42).

CONCLUSIONS

Higher BPA exposure is associated with general and central obesity in the general adult population of the United States. Reverse causation is of concern due to the cross-sectional nature of this study; longitudinal studies are needed to clarify the direction of the association.

Full text, graphs, charts and 46 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747781/

“Animal studies suggest that in utero and early postnatal exposure to this compound may produce a broad range of adverse effects, including **impaired brain development, sexual differentiation, behavior, and immune function, which could extend to future generations.**”

Brain, Behavior And Immunology • August 2011

Epigenetic perspective on the developmental effects of bisphenol A

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Abstract

Bisphenol A (BPA) is an estrogenic environmental toxin widely used in the production of plastics and ubiquitous human exposure to this chemical has been proposed to be a potential risk to public health. Animal studies suggest that in utero and early postnatal exposure to this compound may produce a broad range of adverse effects, including impaired brain development, sexual differentiation, behavior, and immune function, which could extend to future generations. Molecular mechanisms that underlie the long-lasting effects of BPA continue to be elucidated, and likely involve disruption of epigenetic programming of gene expression during development. Several studies have provided evidence that maternal exposure to BPA results in postnatal changes in DNA methylation status and altered expression of specific genes in offspring. However, further studies are needed to extend these initial findings to other genes in different tissues, and to examine the correlations between BPA-induced epigenetic alterations, changes in gene expression, and various phenotypic outcomes. It will be also important to explore whether the epigenetic effects of BPA are related to its estrogenic activity, and to determine which downstream effector proteins could mediate changes in DNA methylation. In this review, we will highlight research indicating a consequence of prenatal BPA exposure for brain, behavior, and immune outcomes and discuss evidence for the role of epigenetic pathways in shaping these developmental effects. Based on this evidence, we will suggest future directions in the study of BPA-induced epigenetic effects and discuss the transgenerational implications of exposure to endocrine disrupting chemicals.

Full text, graphs, charts and 93 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3703316/

Generational poverty leads to poor diet which results in aberrant behavior and impaired brain development.

STOP BUYING FOODS MADE WITH PETROLEUM BASED, CARCINOGENIC, MUTAGENIC, FETOTOXIC, NEUROTOXIC, SYSTEM-WIDE HUMAN SPECIES POISONS AND EVENTUALLY THEY'LL STOP MAKING THEM. THEY MAKE THEM BECAUSE WE BUY THEM.

Plastic waste inputs from land into the ocean in 2010

The 192 countries with a coast bordering Atlantic, Pacific, and Indian oceans, Mediterranean and Black seas produced a total of 2.5 billion metric tons of solid waste. Of that, 275 million metric tons was plastic, and an estimated 8 million metric tons of mismanaged plastic waste entered the ocean in 2010.

Environmental Toxicology And Pharmacology • September 2011

Serum unconjugated bisphenol A concentrations in men may influence embryo quality indicators during in vitro fertilization

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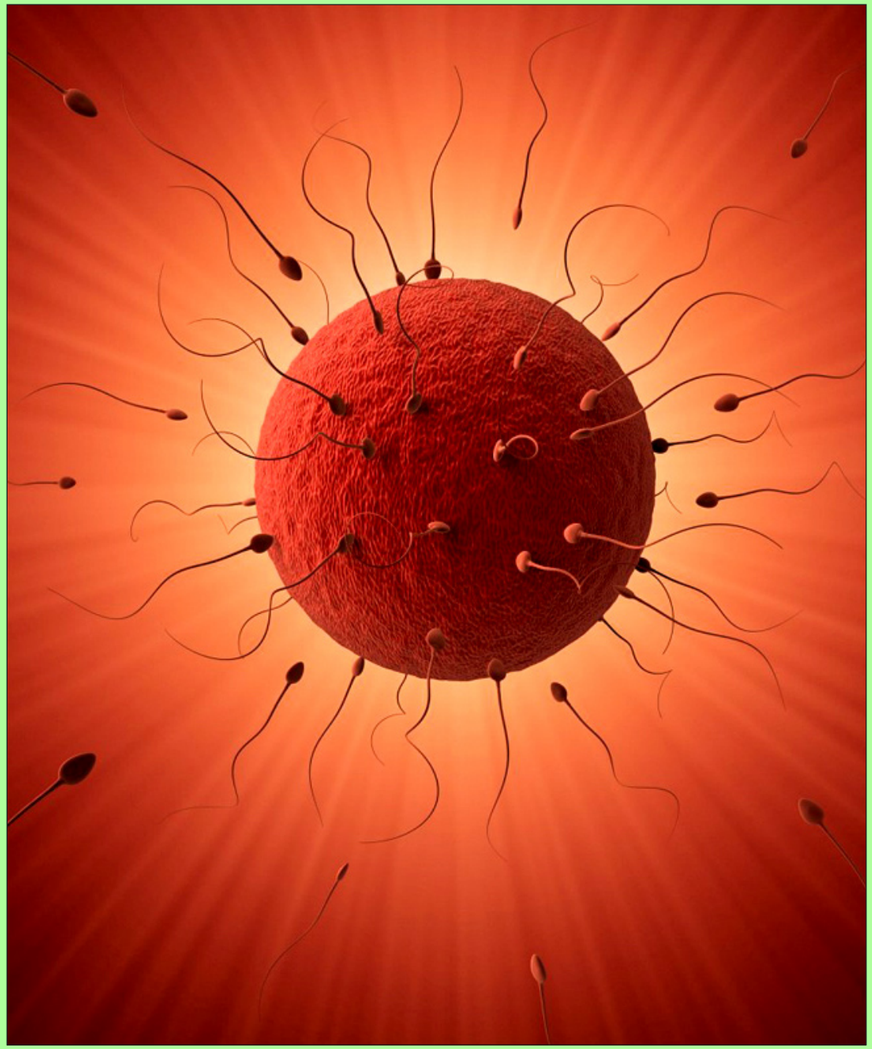
Abstract

"Here we assess bisphenol A (BPA) in couples undergoing in vitro fertilization (IVF) and indicators of embryo quality; embryo cell number (ECN) and embryo fragmentation score (EFS). Twenty-seven couples provided serum on the day of oocyte retrieval. Unconjugated BPA was measured by HPLC with Coularray detection. Odds ratios (OR) were generated using ordinal logistic regression including female and male BPA concentrations, age and race, and day of embryo transfer for ECN. Inverse associations are suggested for male BPA with ECN (OR=0.70, P=0.069), and EFS (OR=0.54, P=0.009), but not for women. Male BPA exposure may affect embryo quality during IVF."

Full text, graphs, charts and 34 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC/3157013/



Neuroscience • May 2010

Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A

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Abstract

The estrogen-mimicking endocrine disrupter bisphenol A (BPA) which is used in the manufacture of plastic and epoxy resins, is one of the world's most heavily produced synthetic chemicals. BPA is detected in animal tissues, and its bio-accumulation has shown to be higher in the fetus than the mother. Exposure to doses below the daily safe limit has been reported to affect the sexual differentiation of the brain and modify the behavior of the exposed rodent offspring. The aim of the present study was to investigate in the rat the possible organizational effects of low BPA exposure on glucocorticoid-regulated responses. Female breeders were exposed to 40 microg/kg b.w. BPA daily throughout pregnancy and lactation. Plasma corticosterone levels and the two types of hippocampal corticosteroid receptors (GR and MR) were determined in mid-adolescent offspring under basal conditions and following a Y-maze task. BPA treated females had higher corticosterone levels than control females and BPA males and lower GR levels than BPA males, under basal conditions. Following the mildly stressful experience of Y-maze, corticosterone levels were increased in BPA-treated animals of both sexes, compared to the controls. GR levels were also increased in BPA-treated females compared to males. No effect of BPA was observed on MR levels, whereas the Y-maze experience significantly decreased receptors' levels in both female groups. The animals' performance in the task was also evaluated. BPA exposure significantly impaired the spatial recognition memory in both sexes, and modified the behavioural coping in a sex-dependent manner. Female BPA-treated offspring exhibited increased "anxiety-like" behaviour and dramatic loss of exploration attitude during the task, in comparison to males. This study provides for the first time evidence that corticosterone and its actions in the brain are sensitive to the programming effects of BPA at a dose below the currently acceptable daily intake.

http://www.ncbi.nlm.nih.gov/pubmed/20219646

"The estrogen-mimicking endocrine disrupter bisphenol A (BPA) which is used in the manufacture of plastic and epoxy resins, is one of the world's most heavily produced synthetic chemicals. BPA is detected in animal tissues, and its bio-accumulation has shown to be higher in the fetus than the mother. Exposure to doses below the daily safe limit has been reported to affect the sexual differentiation of the brain and modify the behavior of the exposed rodent offspring. BPA exposure significantly impaired the spatial recognition memory in both sexes, and modified the behavioural coping in a sex-dependent manner. Female BPA-treated offspring exhibited increased "anxiety-like" behaviour and dramatic loss of exploration attitude during the task, in comparison to males. **This study provides for the first time evidence that corticosterone and its actions in the brain are sensitive to the programming effects of BPA at a dose below the currently acceptable daily intake.**"

“The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology.”

Science • June 2005 • Corrected May 2010

Epigenetic transgenerational actions of endocrine disruptors and male fertility

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Abstract

Transgenerational effects of environmental toxins require either a chromosomal or epigenetic alteration in the germ line. Transient exposure of a gestating female rat during the period of gonadal sex determination to the endocrine disruptors vinclozolin (an antiandrogenic compound) or methoxychlor (an estrogenic compound) induced an adult phenotype in the F1 generation of decreased spermatogenic capacity (cell number and viability) and increased incidence of male infertility. These effects were transferred through the male germ line to nearly all males of all subsequent generations examined (that is, F1 to F4). The effects on reproduction correlate with altered DNA methylation patterns in the germ line. The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology.

Full text, graphs, charts and 25 references

http://science.sciencemag.org/content/sci/308/5727/1466.full.pdf

“Extractability experiments did not enable us to conclude whether BPA passes through the skin, but indicated that it can enter the skin to such a depth that it can no longer be washed off. If this BPA ends up in the human metabolism, exposure of a person repeatedly touching thermal printer paper for 10 h/day, such as at a cash register, could reach 71 microg/day, which is 42 times less than the present tolerable daily intake (TDI). However, if more than just the finger pads contact the BPA-containing paper or a hand cream enhances permeability of the skin, this margin might be smaller.”

Annals Of Bioanalytical Chemistry • September 2010

Transfer of bisphenol A from thermal printer paper to the skin

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Abstract

Of 13 thermal printing papers analyzed, 11 contained 8-17 g/kg bisphenol A (BPA). When taking hold of a receipt consisting of thermal printing paper for 5 s, roughly 1 microg BPA (0.2-6 microg) was transferred to the forefinger and the middle finger if the skin was rather dry and about ten times more if these fingers were wet or very greasy. This amount transferred to dry skin was neither significantly increased when taking hold of the paper at up to 10 sites, nor reduced when BPA-free paper was contacted afterwards. After 60-90 min, BPA applied to the skin as a solution in ethanol was only partially or no longer at all extractable with ethanol, whereas BPA transferred to the skin by holding thermal printer paper remained largely extractable after 2 h. This suggests that penetration of the skin depends on the conditions. Extractability experiments did not enable us to conclude whether BPA passes through the skin, but indicated that it can enter the skin to such a depth that it can no longer be washed off. If this BPA ends up in the human metabolism, exposure of a person repeatedly touching thermal printer paper for 10 h/day, such as at a cash register, could reach 71 microg/day, which is 42 times less than the present tolerable daily intake (TDI). However, if more than just the finger pads contact the BPA-containing paper or a hand cream enhances permeability of the skin, this margin might be smaller.

http://www.ncbi.nlm.nih.gov/pubmed/20623271

“These results suggested that prenatal and lactational BPA-exposure might perturb the neurotransmitter system in adult mice. **Prenatal and lactational exposure to low-doses of bisphenol A alters brain monoamine concentration in adult mice.**”

Neuroscience Letters • October 2010

Prenatal and lactational exposure to low-doses of bisphenol A alters brain monoamine concentration in adult mice

Author information

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Abstract

Bisphenol A (BPA) is an endocrine-disrupting chemical, widely used in industry and dentistry. We have previously reported that BPA affects murine neocortical development by accelerating neuronal differentiation/migration resulting in abnormal neocortical architecture as well as apparent thalamocortical connections in adult mice brains. The aim of this study was to investigate whether or not prenatal and lactational BPA-exposure affects the level of neurotransmitters in mice brains. Pregnant mice were injected subcutaneously with 20μg/kg of BPA daily from embryonic day 0 (E0) until postnatal day 21 (P21). Control animals received a vehicle alone. The brains were removed and dissected into six regions for biochemical assays (n=7-8) at postnatal 3 weeks (P3W) and P10-15W. The concentration of the neurotransmitters was determined by high-performance liquid chromatography. The levels of dopamine and its metabolite significantly increased in the caudate/putamen and dorsal raphe nucleus, whereas serotonin and its metabolite increased in the caudate/putamen, dorsal raphe nucleus, thalamus and Substantia nigra in the BPA-exposure group at both P3W and/or P14-15W. These results suggested that prenatal and lactational BPA-exposure might perturb the neurotransmitter system in adult mice.

http://www.ncbi.nlm.nih.gov/pubmed/20709143

“... urinary BPA may be associated with **declined semen quality and increased sperm DNA damage** ...”

Reproductive Toxicology • December 2010

Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic [see next page]

Author Information

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Abstract

Bisphenol A (BPA) impairs spermatogenesis in animals, but human studies are lacking. We measured urinary BPA concentrations, semen quality, and sperm DNA damage (comet assay) in 190 men recruited through an infertility clinic. BPA was detected in 89% of samples, with a median (interquartile range [IQR]) concentration of 1.3 (0.8–2.5) ng/mL. Urinary BPA concentration was associated with slightly elevated, though not statistically significant, odds for below reference sperm concentration, motility, and morphology. When modeled as continuous dependent variables, an IQR increase in urinary BPA concentration was associated with declines in sperm concentration, motility, and morphology of 23% (95%CI -40%, -0.3%), 7.5% (-17%, +1.5%), and 13% (-26%, -0.1%), respectively, along with a 10% (0.03%, 19%) increase in sperm DNA damage measured as the percentage of DNA in comet tail. In conclusion, urinary BPA may be associated with declined semen quality and increased sperm DNA damage, but confirmatory studies are needed.

Full text, graphs, charts and 34 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2993767/

BPA & SPERM

We've heard a lot of concerning news about the chemical Bisphenol-A in our food supply, water and the air we breathe and how it can have adverse effects on our health, especially for toddlers. A new study raises yet another alarm over BPA — this time on the effects of sperm count and quality. The study found a relationship between BPA levels in urine and decreased sperm concentrations. You're likely already concerned about your child's direct exposure to BPA, but now do you need to think about your (or your husband's) exposure, too?

The study was conducted by researchers from the Harvard and Michigan Schools of Public Health along with the Massachusetts General Hospital and the U.S. Centers for Disease Control and Prevention (CDC). In the study published by the medical journal Reproductive Toxicology, 190 participants gave urine and sperm samples, and 78 men gave follow up samples. The results showed that 89 percent of all urine samples had detectable levels of BPA. The researchers found that samples with higher concentrations also had a correspondingly lower sperm count. Those with the highest levels of BPA had sperm counts on average 23 percent lower than those with the lowest BPA levels and highest sperm count. The study further suggested an increase of 10 percent in DNA damage resulting from elevated BPA levels.

Animal studies have had similar results, and knowing the overall risks associated with BPA, prospective parents should be very cautious with their consumption habits.

You've probably thrown out your plastic refillable water bottles and unsafe resusable water bottles already. You can also greatly reduce your exposure to BPA by replacing shower curtains, avoiding canned foods and food that comes in in No 7 and No 3 plastics, replace all medicines that come in plastic containers into glass containers, eliminate all plastic toys, don't accept cash register receipts unless absolutely necessary and stop reading newspapers, all significant sources of Bishpenol A and Bisphenol analogues like Bisphenol S, Bisphenol F and Bisphenol AF, the ones we don't hear about that are also endocrine disruptors and being used to quietly replace Bishphenol A. You've seen the cans marked "No BPA," right ...

While we certainly hope that the FDA sees the writing on the wall and has an outright ban of Bisphenol A and all of its analogues for all food grade items and children's products, until then parents may want to take extreme caution during inception and the early years of their child's development. Avoid all plastics. Pictured at right, various deformed sperm after exposure to Bisphenol A.

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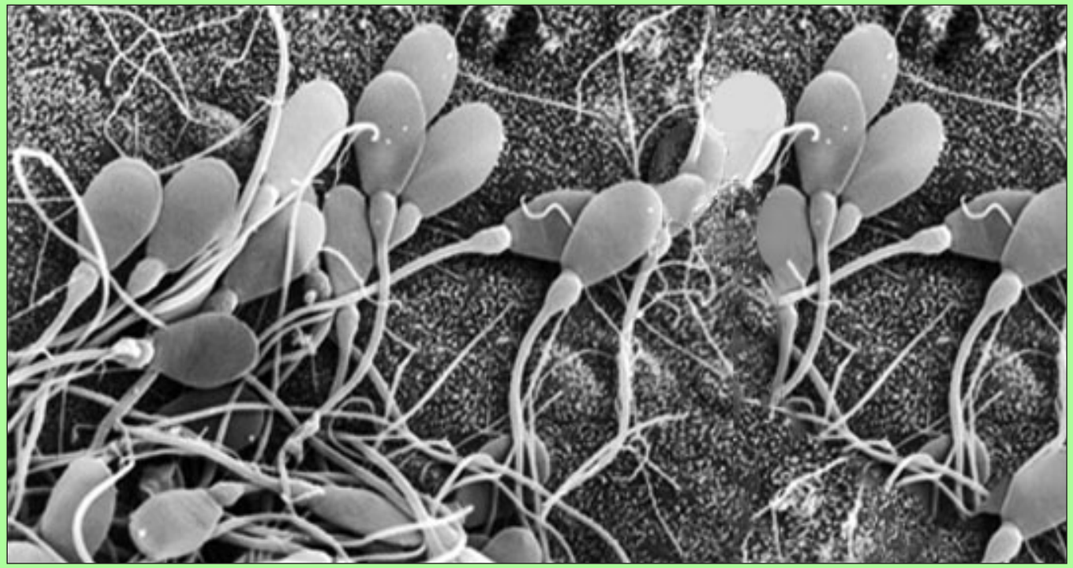

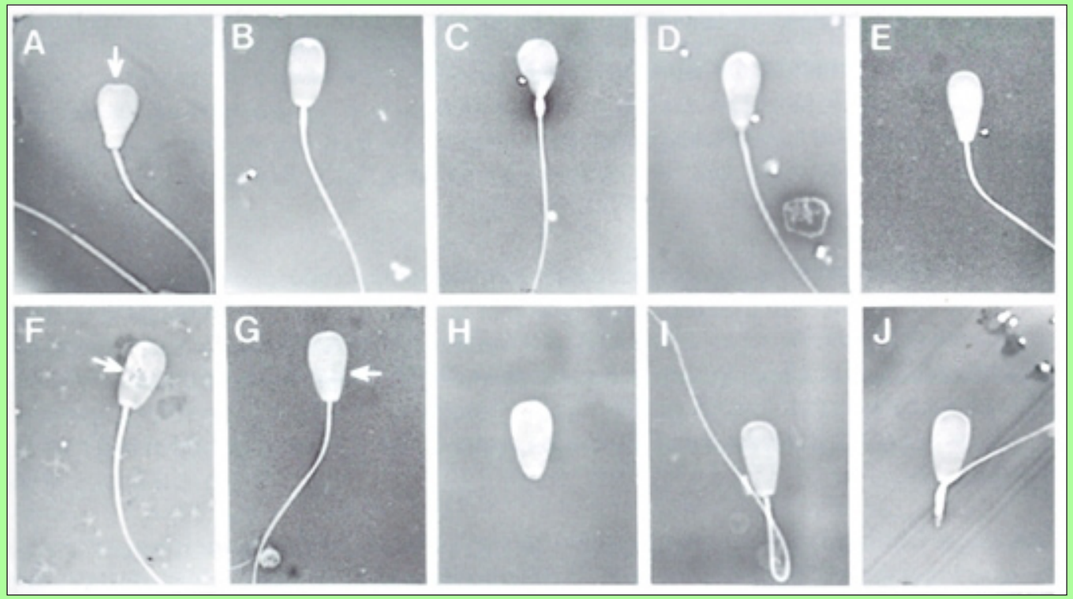

A. Normal Sperm B. Knobbed acrosome (beaded form) C. Pyriform head (severe) D. Pyriform head (moderate) E. Pyriform head (slight) F. Nuclear vacuoles G. Diadem defects H. Detached head I. Distal reflex J. Dag-like defect (broken midpiece).

Journal Of Agriculture And Food Chemistry • February 2009

Levels of bisphenol A in canned soft drink products in Canadian markets

Author information
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Abstract

The method developed previously for the determination of bisphenol A (BPA) in liquid infant formula was adapted and validated for determination of BPA in soft drink products. This method was based on solid phase extraction and derivatization with acetic anhydride followed by gas chromatography-mass spectrometry in selected-ion monitoring mode. The average method detection limit was 0.045 microg/L for a 10 mL sample. The average extraction recoveries were 101 and 99.9% obtained with seven different soft drink products spiked with BPA at 0.5 and 2.5 microg/L, respectively. Good repeatability of the method was observed with replicate analyses of seven different soft drinks; relative standard deviations ranged from 1.3 to 6.6%. This method was used to analyze samples of 72 canned soft drink products for BPA. Except for three products from which BPA-d16 could not be recovered at all due to interference of product compositions (e.g., quinine hydrochloride in tonic water), BPA was detected in samples of all the other products at levels ranging from 0.032 to 4.5 microg/L. About 75% of the products had BPA levels of <0.5 microg/L, and 85% of the products had BPA levels of <1 microg/L. Exposure to BPA through consumption of canned soft drink products is low; dietary intake of BPA was estimated at 0.027 microg/kg of body weight/day on the basis of the consumption of one canned soft drink with the highest BPA level (4.5 microg/L) for an adult with a 60 kg body weight, well below the provisional tolerable daily intake of 25 microg/kg of body weight/day established by Health Canada.

http://www.ncbi.nlm.nih.gov/pubmed/19170636

Environmental Health Perspectives • October 2009

Perinatal exposure to bisphenol a alters early adipogenesis in the rat

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Abstract

BACKGROUND

The causes of the current obesity pandemic have not been fully elucidated. Implication of environmental endocrine disruptors such as bisphenol A (BPA) on adipose tissue development has been poorly investigated.

OBJECTIVES

The aim of the present study was to evaluate the effects of perinatal exposure to BPA on early adipose storage at weaning.

METHODS

Pregnant Sprague-Dawley rats had access to drinking water containing 1 mg/L BPA from day 6 of gestation through the end of lactation. Pups were weaned on postnatal day (PND) 21. At that time, we investigated perigonadal adipose tissue of pups (weight, histology, gene expression). For the remaining animals, we recorded body weight and food intake for animals on either standard chow or a high-fat diet.

RESULTS

Gestational exposure to BPA did not alter the sex ratio or litter size at birth. On PND1, the weight of male and female BPA-exposed pups was increased. On PND21, body weight was increased only in females, in which parametrial white adipose tissue (pWAT) weight was increased about 3-fold. This excess of pWAT was associated with adipocyte hypertrophy and overexpression of lipogenic genes such as C/EBP-alpha (CAAT enhancer binding protein alpha), PPAR-gamma (peroxisome proliferator-activated receptor gamma), SREBP-1C (sterol regulatory element binding protein-1C), LPL (lipoprotein lipase), FAS (fatty acid synthase), and SCD-1 (stearoyl-CoA desaturase 1). In addition, gene expression of SREBP-1C, FAS, and ACC (acetyl-CoA carboxylase) was also increased in liver from BPA-exposed females at PND21, without a change in circulating lipids and glucose. After weaning, perinatal BPA exposure predisposed to overweight in a sex- and diet-dependent manner. We observed no change in food intake due to perinatal BPA exposure in rats on either standard chow or a high-fat diet.

CONCLUSIONS

Perinatal exposure to a low dose of BPA increased adipogenesis in females at weaning. Adult body weight may be programmed during early life, leading to changes dependent on the sex and the nutritional status. Although further studies are required to understand the mechanisms of BPA action in early life, these results are particularly important with regard to the increasing prevalence of childhood obesity and the context-dependent action of endocrine disruptors.

Full text, PDF, graphs, charts and 56 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2790509/pdf/ehp-117-1549.pdf

“The causes of **the current obesity pandemic** have not been fully elucidated. Implication of environmental endocrine disruptors such as bisphenol A (BPA) on adipose tissue development has been poorly investigated. Perinatal exposure to a low dose of BPA increased adipogenesis in females at weaning. Adult body weight may be programmed during early life, leading to changes dependent on the sex and the nutritional status. Although further studies are required to understand the mechanisms of BPA action in early life, these results are particularly important with regard to the increasing prevalence of childhood obesity and the context dependent action of endocrine disruptors.”

Journal Of AOAC International • November 2009\

Levels of bisphenol A diglycidyl ether (BADGE) and bisphenol F diglycidyl ether (BFDGE) in canned liquid infant formula products in Canada and dietary intake estimates

Author information

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Abstract

A method based on solid-phase extraction followed by HPLC analysis with fluorescence detection was developed for the determination of bisphenol A diglycidyl ether (BADGE) and bisphenol F diglycidyl ether (BFDGE) in liquid infant formula. In this method, instead of trying to isolate and measure each individual form of the molecules, hydrolysis of BADGE, BFDGE, BADGE x H2O, and BFDGE x H2O was forced to completion to their stable forms, BADGE x 2H2O and BFDGE x 2H2O, before extraction. The method LODs were 2.0 ng/g for BADGE and 3.0 ng/g for BFDGE. Extraction recoveries were 61-91% for BADGE, and 55-82% for BFDGE over the concentration range of 10 to 50 ng/g. The method was used to analyze samples of 21 canned liquid infant formula products for BADGE and BFDGE. BADGE was detected in samples of all products at levels ranging from as low as 2.4 ng/g to as high as 262 ng/g. BFDGE was detected in only one product (40 ng/g), and this product also had the highest BADGE level (262 ng/g). HPLC/MS/MS with a similar LOD was also used to confirm the results. The probable daily intakes (PDI) of BADGE and BFDGE due to consumption of canned liquid infant formula were estimated for infants from premature to 12-18 months of age. The maximum PDI of BADGE was 22 microg/kg body weight/day for the 12-18 months old with the maximum formula intake. The maximum PDI of BFDGE was < 3.4 microg/kg body weight/day.

http://www.ncbi.nlm.nih.gov/pubmed/20166597

“BPA was found to migrate from polycarbonate water bottles at rates ranging from 0.20 ng/h to 0.79 ng/h. At room temperature the migration of BPA was independent of whether or not the bottle had been previously used. Exposure to boiling water (100 degrees C) increased the rate of BPA migration by up to **55-fold**.”

Toxicology Letters • January 2008

Bisphenol A is released from polycarbonate drinking bottles and mimics the neurotoxic actions of estrogen in developing cerebellar neurons

Author Information
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Abstract

The impact of endocrine disrupting chemical (EDC) exposure on human health is receiving increasingly focused attention. The prototypical EDC bisphenol A (BPA) is an estrogenic high-production chemical used primarily as a monomer for the production of polycarbonate and epoxy resins. It is now well established that there is ubiquitous human exposure to BPA. In the general population, exposure to BPA occurs mainly by consumption of contaminated foods and beverages that have contacted epoxy resins or polycarbonate plastics. To test the hypothesis that bioactive BPA was released from polycarbonate bottles used for consumption of water and other beverages, we evaluated whether BPA migrated into water stored in new or used high-quality polycarbonate bottles used by consumers. Using a sensitive and quantitative competitive enzyme-linked immunosorbent assay, BPA was found to migrate from polycarbonate water bottles at rates ranging from 0.20 ng/h to 0.79 ng/h. At room temperature the migration of BPA was independent of whether or not the bottle had been previously used. Exposure to boiling water (100 degrees C) increased the rate of BPA migration by up to 55-fold. The estrogenic bioactivity of the BPA-like immunoreactivity released into the water samples was confirmed using an in vitro assay of rapid estrogen signaling and neurotoxicity in developing cerebellar neurons. The amounts of BPA found to migrate from polycarbonate drinking bottles should be considered as a contributing source to the total “EDC-burden” to which some individuals are exposed.

Full text, graphs, charts and 21 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2254523/

“Bisphenol A (BPA) is widely used in epoxy resins lining food and beverage containers.
Evidence of effects in animals has generated concern over low-level chronic exposures in humans ...
BPA exposure, reflected in higher urinary concentrations of BPA, may be associated with
avoidable morbidity in the community-dwelling adult population.”

JAMA • September 2008

Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults

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Abstract

CONTEXT:
Bisphenol A (BPA) is widely used in epoxy resins lining food and beverage containers. Evidence of effects in animals has generated concern over low-level chronic exposures in humans.

MAIN OUTCOME MEASURES
Chronic disease diagnoses plus blood markers of liver function, glucose homeostasis, inflammation, and lipid changes.

RESULTS
Higher urinary BPA concentrations were associated with cardiovascular diagnoses in age-, sex-, and fully adjusted models (OR per 1-SD increase in BPA concentration, 1.39; 95% confidence interval [CI], 1.18-1.63; P = .001 with full adjustment). Higher BPA concentrations were also associated with diabetes (OR per 1-SD increase in BPA concentration, 1.39; 95% confidence interval [CI], 1.21-1.60; P < .001) but not with other studied common diseases. In addition, higher BPA concentrations were associated with clinically abnormal concentrations of the liver enzymes gamma-glutamyltransferase (OR per 1-SD increase in BPA concentration, 1.29; 95% CI, 1.14-1.46; P < .001) and alkaline phosphatase (OR per 1-SD increase in BPA concentration, 1.48; 95% CI, 1.18-1.85; P = .002).

CONCLUSION
Higher BPA exposure, reflected in higher urinary concentrations of BPA, may be associated with avoidable morbidity in the community-dwelling adult population.

http://www.ncbi.nlm.nih.gov/pubmed/18799442/

Environmental Research • October 2008

Effects of developmental exposure to bisphenol A on brain and behavior in mice

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Abstract

Bisphenol A (BPA) is a widespread estrogenic chemical used in the production of polycarbonate, and epoxy resins lining food and beverage cans and in dental sealants. During fetal life the intrauterine environment is critical for the normal development, and even small changes in the levels of hormones, such as estradiol or estrogen-mimicking chemicals, can lead to changes in brain function and consequently in behavior. We review here a series of ethological studies on the effects of maternal oral exposure during the last part of gestation (prenatal exposure) or from gestation day 11 to postnatal day 7 (perinatal exposure) to a low, environmentally relevant dose of BPA (10 microg/kg bw/day) on behavioral responses of CD-1 mouse offspring. We examined both male and female offspring and found that maternal exposure to BPA affected: (1) behavioral responses to novelty before puberty and, as adults; (2) exploration and activity in a free-exploratory open field; (3) exploration in the elevated plus maze and (4) sensitivity to amphetamine-induced reward in the conditioned place preference test. A consistent effect of the maternal exposure to BPA is that in all these different experimental settings, while a significant sex difference was observed in the control group, exposure to BPA decreased or eliminated the sex difference in behavior. In addition, exposure of female mice to BPA in both adulthood or during fetal life altered subsequent maternal behavior. These findings, together with those from other laboratories, are evidence of long-term consequences of maternal exposure to low-dose BPA at the level of neurobehavioral development.

http://www.ncbi.nlm.nih.gov/pubmed/18949834

“During fetal life the intrauterine environment is critical for the normal development, and **even small changes in the levels of hormones, such as estradiol or estrogen-mimicking chemicals, can lead to changes in brain function and consequently in behavior** ... [with] a low, environmentally relevant dose of BPA (10 microg/kg bw/day) on behavioral responses of CD-1 mouse offspring [were examined] ... maternal exposure to BPA affected: (1) behavioral responses to novelty before puberty and, as adults; (2) exploration and activity in a free-exploratory open field; (3) exploration in the elevated plus maze and (4) sensitivity to amphetamine-induced reward in the conditioned place preference test.

These findings, together with those from other laboratories, are **evidence of long-term consequences of maternal exposure to low-dose BPA** at the level of neurobehavioral development.”

Journal Of Chromatography • February 2006

Determination of bisphenol diglycidyl ether residues in canned foods by pressurized liquid extraction and liquid chromatography-tandem mass spectrometry

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Abstract

A new confirmatory method for simultaneous determination of bisphenol diglycidyl ether residues (BADGE, BADGE.H(2)O, BADGE.2H(2)O, BADGE.H(2)O.HCl, BADGE.HCl, BADGE.2HCl, BFDGE and BFDGE.2HCl) from canned food has been developed. The proposed method includes extraction by pressurized liquid extraction (PLE) followed by liquid-liquid partition and purification by solid phase extraction (SPE). Several solvent systems and different operating conditions (time, temperature) have been investigated for PLE optimization. A reversed-phase high-performance liquid chromatography (RP-HPLC) coupled to atmospheric pressure chemical ionisation tandem mass spectrometry (APCI-MS-MS) method was developed for the separation, quantification and confirmation. The ion source settings were optimized using a design of experiments (DOE). The optimized method was applied to the determination of these chemicals at very low levels in different samples with a quantification limit of 5 ng/g. Recoveries ranged between 82 and 101% and standard deviations were less than 10%.

http://www.ncbi.nlm.nih.gov/pubmed/16376905

“Estrogenic endocrine disruptors (EEDs) are naturally occurring or man-made compounds present in the environment that are able to bind to estrogen receptors and interfere with normal cellular development in target organs and tissues. The present findings are evidence of **long-term consequences of developmental exposure to BPA** ... on neurobehavioral development ...”

Hormones & Behavior • September 2007

Developmental exposure to low-dose estrogenic endocrine disruptors alters sex differences in exploration and emotional responses in mice

Author information

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Abstract

Estrogenic endocrine disruptors (EEDs) are naturally occurring or man-made compounds present in the environment that are able to bind to estrogen receptors and interfere with normal cellular development in target organs and tissues. There is mounting evidence that EEDs can interfere with the processes of sexual differentiation of brain and behavior in different animal models. We investigated the effects of maternal exposure to EEDs, at concentrations within the range of human exposure and not patently teratogenic, on behavioral responses of male and female house mice (Mus musculus domesticus) before and after puberty. Pregnant dams were trained to spontaneously drink daily doses of corn oil with or without the estrogenic plastic derivative, bisphenol A (BPA 10 microg/kg), or the estrogenic insecticide methoxychlor (MXC 20 microg/kg) from gestation day 11 to postpartum day 8. Their male and female offspring were examined at different ages to examine several components of explorative and emotional behaviors in 3 experimental paradigms: a novelty test before puberty and, as adults, a free-exploratory open-field test and the elevated plus maze test. The main results are sex differences in control mice on a number of behavioral responses at both ages and in all experimental paradigms, while perinatal exposure to BPA or MXC decreased or eliminated such sex differences. The present findings are evidence of long-term consequences of developmental exposure to BPA and MXC on neurobehavioral development and suggest a differential effect of low-dose exposure to these estrogenic chemicals in males and females.

http://www.ncbi.nlm.nih.gov/pubmed/17568585

Endocrinology • June 2006

Large effects from small exposures III
Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure

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Abstract

Over 6 billion pounds per year of the estrogenic monomer bisphenol A (BPA) are used to manufacture polycarbonate plastic products, in resins lining metal cans, in dental sealants, and in blends with other types of plastic products. The ester bond linking BPA molecules in polycarbonate and resins undergoes hydrolysis, resulting in the release of free BPA into food, beverages, and the environment, and numerous monitoring studies now show almost ubiquitous human exposure to biologically active levels of this chemical. BPA exerts estrogenic effects through the classical nuclear estrogen receptors, and BPA acts as a selective estrogen receptor modulator. However, BPA also initiates rapid responses via estrogen receptors presumably associated with the plasma membrane. Similar to estradiol, BPA causes changes in some cell functions at concentrations between 1 pM and 1 nM, and the mean and median range of unconjugated BPA measured by multiple techniques in human pregnant maternal, fetal, and adult blood and other tissues exceeds these levels. In contrast to these published findings, BPA manufacturers persist in describing BPA as a weak estrogen and insist there is little concern with human exposure levels. Our concern with human exposure to BPA derives from 1) identification of molecular mechanisms mediating effects in human and animal tissues at very low doses, 2) in vivo effects in experimental animals caused by low doses within the range of human exposure, and 3) widespread human exposure to levels of BPA that cause adverse effects in animals.

“Over 6 billion pounds per year of the estrogenic monomer bisphenol A (BPA) are used to manufacture polycarbonate plastic products, in resins lining metal cans, in dental sealants, and in blends with other types of plastic products. The ester bond linking BPA molecules in polycarbonate and resins undergoes hydrolysis, resulting in the release of free BPA into food, beverages, and the environment, and numerous monitoring studies now show almost ubiquitous human exposure to biologically active levels of this chemical. BPA exerts estrogenic effects through the classical nuclear estrogen receptors, and BPA acts as a selective estrogen receptor modulator. However, BPA also initiates rapid responses via estrogen receptors presumably associated with the plasma membrane.”

http://www.ncbi.nlm.nih.gov/pubmed/16690810

Environmental Health Perspectives • August 2005

An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment

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Abstract

Bisphenol A (BPA) is the monomer used to manufacture polycarbonate plastic, the resin lining of cans, and other products, with global capacity in excess of 6.4 billion lb/year. Because the ester bonds in these BPA-based polymers are subject to hydrolysis, leaching of BPA has led to widespread human exposure. A recent report prepared by the Harvard Center for Risk Analysis and funded by the American Plastics Council concluded that evidence for low-dose effects of BPA is weak on the basis of a review of only 19 studies; the report was issued after a delay of 2.5 years. A current comprehensive review of the literature reveals that the opposite is true. As of December 2004, there were 115 published in vivo studies concerning low-dose effects of BPA, and 94 of these report significant effects. In 31 publications with vertebrate and invertebrate animals, significant effects occurred below the predicted "safe" or reference dose of 50 microg/kg/day BPA. An estrogenic mode of action of BPA is confirmed by in vitro experiments, which describe disruption of cell function at 10(-12) M or 0.23 ppt. Nonetheless, chemical manufacturers continue to discount these published findings because no industry-funded studies have reported significant effects of low doses of BPA, although > 90% of government-funded studies have reported significant effects. Some industry-funded studies have ignored the results of positive controls, and many studies reporting no significant effects used a strain of rat that is inappropriate for the study of estrogenic responses. We propose that a new risk assessment for BPA is needed based on a) the extensive new literature reporting adverse effects in animals at doses below the current reference dose; b) the high rate of leaching of BPA from food and beverage containers, leading to widespread human exposure; c) reports that the median BPA level in human blood and tissues, including in human fetal blood, is higher than the level that causes adverse effects in mice; and d) recent epidemiologic evidence that BPA is related to disease in women.

Full text, graphs, charts and 65 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1280330/

"A recent report prepared by the Harvard Center for Risk Analysis and funded by the American Plastics Council concluded that evidence for low-dose effects of BPA is weak on the basis of a review of only 19 studies; the report was issued after a delay of 2.5 years. A current comprehensive review of the literature reveals that the opposite is true. **As of December 2004, there were 115 published in vivo studies concerning low-dose effects of BPA, and 94 of these report significant effects. In 31 publications with vertebrate and invertebrate animals, significant effects occurred below the predicted "safe" or reference dose of 50 microg/kg/day BPA**. An estrogenic mode of action of BPA is confirmed by in vitro experiments, which describe disruption of cell function at 10(-12) M or 0.23 ppt. **Nonetheless, chemical manufacturers continue to discount these published findings because no industry-funded studies have reported significant effects of low doses of BPA, although > 90% of government-funded studies have reported significant effects**."

A New Risk Assessment For BPA Is Needed Based On:

"a) the extensive new literature reporting adverse effects in animals at doses below the current reference dose; b) the high rate of leaching of BPA from food and beverage containers, leading to widespread human exposure; c) reports that the median BPA level in human blood and tissues, including in human fetal blood, is higher than the level that causes adverse effects in mice; and d) recent epidemiologic evidence that BPA is related to disease in women."

Endocrine • November 2004

Adverse effects of environmental toxicants, octylphenol and bisphenol A, on male reproductive functions in pubertal rats

Author information
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Abstract

It has been proposed that a global decline in sperm counts, semen quality, and several male reproductive disorders are associated with exposure to environmental chemicals. Thus, the present study examined the effects of two estrogenic chemicals, octylphenol (OP) and bisphenol A (BPA), on epididymal sperm counts and sperm motility, luteinizing hormone (LH)-releasing hormone (LHRH)-stimulated plasma LH and steroid hormones, insulin-like growth factor I (IGF-I), and accessory reproductive organs in pubertal male Wistar rats. Fifty-day-old rats in the OP group (n=11) and BPA group (n=11) received daily sc injections of the respective chemical at a dose of 3 mg/kg bw dissolved in 0.2 mL DMSO. Rats in the control group (DMSO group; n=10) received 0.2 mL DMSO alone. After 2 wk of treatment, a jugular blood sample was taken, and, on the next day, a second blood sample was taken 1 h after an sc injection of LHRH (250 ng). After 5 wk of treatment, rats were deeply anesthetized and heart blood was collected. Epididymal sperm motility and sperm head counts were determined. LHRH increased plasma LH to higher levels in all groups, but the increases were significant ($p<0.01$) in the BPA and OP groups. However, despite higher LH levels after LHRH injection, the incremental responses of testosterone and pro-gesterone in the OP and BPA groups were small compared to those in the DMSO group, which showed a small LH response. After 5 wk of treatment, plasma testosterone levels were significantly ($p<0.01$) reduced in the OP and BPA groups and this was accompanied by reduced ($p<0.05$) epididymal sperm counts. However, the chemical-treated groups had high basal progesterone levels. No significant effects of chemicals on sperm motility parameters were noted. The chemical-induced increases ($p<0.05$) of the weight of ventral prostate gland were coincided with elevated plasma IGF-I levels in the BPA ($p<0.05$) and OP ($p<0.01$) groups. The present results demonstrated that OP and BPA can reduce sperm counts resulting from lowered plasma testosterone in male rats just after puberty. The enlarged ventral prostate gland may possibly be associated with increased plasma IGF-I, raising the possibility of a link between these chemicals and prostate diseases because IGF-I has been implicated in the pathogenesis of human prostate cancers.

http://www.ncbi.nlm.nih.gov/pubmed/15711031

“It has been proposed that a global decline in sperm counts, semen quality, and several male reproductive disorders are associated with exposure to environmental chemicals. The present results demonstrated that OP and **BPA can reduce sperm counts** resulting from lowered plasma testosterone in male rats just after puberty. The enlarged ventral prostate gland may possibly be associated with increased plasma IGF-I, raising the possibility of a link between these chemicals and prostate diseases because IGF-I has been **implicated in the pathogenesis of human prostate cancers.**”

“These results show that Bisphenol A when given during the neonatal period **caused changes in female reproductive organs.**”

Reproductive Toxicology • May 2003

Changes in reproductive organs of female rats treated with bisphenol A during the neonatal period

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Abstract

The effects of neonatal administration of estrogenic agents on rat reproductive organs were examined. Either bisphenol A (BPA; 0.25, 1, or 4mg/pup) or 10 micro g 17beta-estradiol (E(2)) was given subcutaneously to Sprague-Dawley female rats during the neonatal period from post-natal day (PND) 0 to 9. Animals ovariectomized at 80 days were given subcutaneous injections of 1 micro g/kg E(2) for 3 days from PND 94 to 96. Clefts in the clitoris, early vaginal opening, irregular estrous cycles, a decrease in the area occupied by the corpora lutea (CL) in the ovary, and multiple cystic follicles in the ovary were found in the animals treated neonatally with 1mg BPA. Uterine fluid weight measured after E(2) treatment on PND 94-96 was less than controls. In addition to these abnormalities, unusual body weight gains, persistent vaginal cornification, and lack of CL were observed in females treated neonatally with 4mg BPA. The ovary weight on PND 80 and uterine fluid weight measured after E(2) treatment on PND 94-96 were less than controls for the 4mg BPA group. Neonatal treatment with 10 micro g E(2) induced similar abnormalities as found in the 4mg BPA group. These results show that BPA when given during the neonatal period caused changes in female reproductive organs.

http://www.ncbi.nlm.nih.gov/pubmed/12759096

“These results indicate that the onset of **cytotoxicity caused by BPA** may depend on the intracellular energy status and that mitochondria are important targets of the compound.”

Archives In Toxicology • April 2000

Metabolism and cytotoxicity of bisphenol A and other bisphenols in isolated rat hepatocytes

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Abstract

The relation between the metabolism and the cytotoxic effects of bisphenol A (BPA, 2,2-bis(4-hydroxyphenyl)propane) has been studied in freshly isolated rat hepatocytes and isolated hepatic mitochondria. The incubation of hepatocytes with BPA (0.25-1.0 mM) elicited a concentration- and time-dependent cell death, accompanied by losses of intracellular ATP and total adenine nucleotide pools. BPA at a low-toxic level (0.25 mM) in the hepatocyte suspensions was rapidly converted to its major conjugate, BPA-glucuronide, and other minor products without marked loss of cell viability, although at a toxic level (0.5 mM), more than 65% of the compound presented in an unaltered form 2 h after the incubation. Addition of salicylamide (2 mM), non-toxic to hepatocytes during the incubation period, enhanced BPA-induced cytotoxicity and reduced the loss of BPA and the formation of BPA-glucuronide. The addition of BPA to isolated hepatic mitochondria caused a concentration (0-0.5 mM)-dependent increase in the rate of state 4 oxygen consumption in the presence of an FAD-linked substrate (succinate), indicating an uncoupling effect, whereas the rate of state 3 oxygen consumption was inhibited by BPA. Further, the addition of BPA (0.25 mM) reduced state 3 respiration with NAD+-linked substrates (pyruvate plus malate) and/or with the FAD-linked substrate, whereas state 3 respiration with ascorbate plus tetramethyl-p-phenylenediamine (cytochrome oxidase-linked respiration) was not significantly affected by BPA. A comparative study of the toxic effects of BPA and some bisphenols on cell viability (at 1.0 mM) and mitochondrial respiration (at 0.25 mM) revealed that 4,4’-(1,2-diethyl-1,2-ethenediyl)bisphenol (diethylstilbestrol) was more toxic than BPA, followed by 4,4’-methylenediphenol and 4,4’-biphenol. These results indicate that the onset of cytotoxicity caused by BPA may depend on the intracellular energy status and that mitochondria are important targets of the compound. The toxicity caused by the inhibition of ATP synthesis may be related to the concentration of unmetabolised free BPA remaining in the cell suspensions. In addition, the toxic potency of bisphenols to hepatocytes and mitochondria depends on the relative elongation and/or molecular size of the hydrocarbon bridge between the phenolic groups.

http://www.ncbi.nlm.nih.gov/pubmed/10839477

“Consequences of these multitypes of attack on the nuclei of cells could be (1) nuclear toxicity/cell death; (2) repair of all the hits and then acting as normal cells; or (3) sustaining most of the hits and acting as unstable cells. Proliferation of the last type of cell **is expected to result in transformed cells.**”

Journal Of Toxicology And Environmental Health • January 1997

Biochemical and molecular changes at the cellular level in response to exposure to environmental estrogen-like chemicals

Author information
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Abstract

Estrogen-like chemicals are unique compared to nonestrogenic xenobiotics, because in addition to their chemical properties, the estrogenic property of these compounds allows them to act like sex hormones. Whether weak or strong, the estrogenic response of a chemical, if not overcome, will add extra estrogenic burden to the system. At elevated doses, natural estrogens and environmental estrogen-like chemicals are known to produce adverse effects. The source of extra or elevated concentration of estrogen could be either endogenous or exogenous. The potential of exposure for humans and animals to environmental estrogen-like chemicals is high. Only a limited number of estrogen-like compounds, such as diethylstilbestrol (DES), bisphenol A, nonylphenol, polychlorinated biphenyls (PCBs), and dichlorodiphenyltrichloroethane (DDT), have been used to assess the biochemical and molecular changes at the cellular level. Among them, DES is the most extensively studied estrogen-like chemical, and therefore this article is focused mainly on DES-related observations. In addition to estrogenic effects, environmental estrogen-like chemicals produce multiple and multitype genetic and/or nongenetic hits. Exposure of Syrian hamsters to stilbene estrogen (DES) produces several changes in the nuclei of target organ for carcinogenesis (kidney): (1) Products of nuclear redox reactions of DES modify transcription regulating proteins and DNA; (2) transcription is inhibited; (3) tyrosine phosphorylation of nuclear proteins, including RNA polymerase II, p53, and nuclear insulin-like growth factor-1 receptor, is altered; and (4) DNA repair gene DNA polymerase beta transcripts are decreased and mutated. Exposure of Noble rats to DES also produces several changes in the mammary gland: proliferative activity is drastically altered; the cell cycle of mammary epithelial cells is perturbed; telomeric length is attenuated; etc. It appears that some other estrogenic compounds, such as bisphenol A and nonylphenol, may also follow a similar pattern of effects to DES, because we have recently shown that these compounds alter cell cycle kinetics, produce telomeric associations, and produce chromosomal aberrations. Like DES, bisphenol A after metabolic activation is capable of binding to DNA. However, it should be noted that a particular or multitype hit(s) will depend upon the nature of the environmental estrogen-like chemical. The role of individual attack leading to a particular change is not clear at this stage. Consequences of these multitypes of attack on the nuclei of cells could be (1) nuclear toxicity/cell death; (2) repair of all the hits and then acting as normal cells; or (3) sustaining most of the hits and acting as unstable cells. Proliferation of the last type of cell is expected to result in transformed cells.

http://www.ncbi.nlm.nih.gov/pubmed/9015129

“The proliferative activity of epithelial cells was increased by 143% over controls by the exposure of animals to the low dose of bisphenol A, whereas a 220% increase over controls was observed for the high dose of bisphenol A ... its influence on proliferative activity in the epithelial cells of the mammary gland was profound. The weak estrogenic activity of bisphenol A does not explain its profound effect on cell proliferation observed in this study. **Perturbation of the cell cycle is considered a risk factor for the development of cancer.**”

Journal Of Steroid Biochemistry And Molecular Biology • January 1997

Profound effects of the weak environmental estrogen-like chemical bisphenol A on the growth of the mammary gland of Noble rats

Author information
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Abstract

In the present study we have examined the effects of the environmental estrogenic chemical bisphenol A on proliferative activity, cell cycle kinetics and differentiation of the mammary gland of female Noble rats. Differentiation measured by the degree of lobular maturation revealed that the conversion of immature structures to mature structures was significantly increased in response to exposure to both low (0.1 mg/kg/day) and high (54 mg/kg/day) doses of bisphenol A compared to controls. The proliferative activity of epithelial cells was increased by 143% over controls by the exposure of animals to the low dose of bisphenol A, whereas a 220% increase over controls was observed for the high dose of bisphenol A. The labelling index and growth fraction were 19% and 27%, respectively, for a low dose of bisphenol A; and 27% and 45%, respectively, for a high dose of bisphenol A, compared to 18% and 31%, respectively, in controls. A significant increase in the conversion of mammary epithelial cells from G0, to G1, and S-phase cells by 1.8 and 4.5-fold, respectively, was observed in animals exposed to the high dose of bisphenol A compared to that of controls. Based on the previously reported estrogenic activity of an equivalent dose of bisphenol A to that of diethylstilbestrol (DES) (0.1 mg/kg/day), a calculated theoretical dose of the order of 10(6)-fold higher of bisphenol A will be required to produce the same biological effects as DES. A comparison of the proliferative activity of DES and that of an equivalent dose of bisphenol A observed in this study, however, revealed that its influence on proliferative activity in the epithelial cells of the mammary gland was profound. The weak estrogenic activity of bisphenol A does not explain its profound effect on cell proliferation observed in this study. Perturbation of the cell cycle is considered a risk factor for the development of cancer. Bisphenol-mediated perturbation of the cell cycle in epithelial cells may produce adverse effects in the mammary glands of Noble rats.

http://www.ncbi.nlm.nih.gov/pubmed/9182870

CHAPTER FOUR

TBHQ • *tert*-Butylhydroquinone or tertiary butylhydroquinone

The Peer Review

Tert-Butylhydroquinone, tBHQ or tertiary butylhydroquinone is an aromatic organic compound which is a type of phenol. It is a derivative of hydroquinone, substituted with a tert-butyl group.

TBHQ is a highly effective antioxidant but it's an antioxidant that we definitely don't need in the foods we consume because it's also toxic. It's used as a preservative for unsaturated vegetable oils and many edible animal fats. It does not cause discoloration even in the presence of iron, and does not change the flavor or odor of the material to which it is added. It can also be combined with other toxic preservatives such as propyl gallate, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT). As a food additive, its E number is E319. It is added to a wide range of foods, with the highest limit (1 gram/kg) permitted for frozen fish and fish products. Its primary advantage is extending storage life.

It is used industrially as a stabilizer to inhibit autopolymerization of organic peroxides. It is also used as a corrosion inhibitor in biodiesel. In perfumery, it's used as a fixative to lower the evaporation rate and improve stability. It's also added to varnishes, lacquers, resins and oil-field production chemical compounds.

According to the Centers for Science in the Public Interest (CSPI), a well-designed government study found that this additive increased the incidence of tumors in rats. And according to the National Library of Medicine (NLM), cases of vision disturbances have been reported when humans consume tBHQ. They also cite studies that have found tBHQ to cause liver enlargement, neurotoxic effects, convulsions, and paralysis in laboratory animals.

Some believe BHA and TBHQ also affect human behavior. It's this belief that has landed the ingredients on the black list of the Feingold diet, a dietary approach to managing attention deficit and hyperactivity disorder (ADHD). Advocates of this diet say that those who struggle with their behavior should avoid tBHQ.

The FDA considers tBHQ to be safe, particularly in low amounts, and low-dose TBHQ is particularly problematic. Some research indicates that Americans are getting more than they should and that the "low dose" recommendations are inaccurate and should be revised.

An evaluation by the World Health Organization found that the "average" intake of TBHQ in the United States to be around 0.62 mg/kg of body weight. That's about 90 percent of the acceptable daily intake. Consumption of TBHQ was at 1.2 mg/kg of body weight in those who eat high fat diets and Fast Foods. That's a whopping 180 percent of the acceptable daily intake.

TBHQ, like many questionable food preservatives, is found in processed foods meant to withstand a long shelf life. Avoiding these packaged foods and opting for fresh ingredients is a surefire way to remove this toxic processed food ingredient from your diet.

TBHQ, can be classified as a medicine. On the good side, it has powerful antioxidant and neuroprotective properties at the cellular level. It's been repeatedly shown to alleviate early brain injury and its related cognitive dysfunction, it's been shown to attenuate cerebral oxidative stress under stress induced conditions and it's been used to ameliorate oxidative fluoride-induced stress acting as a neuroprotectant. It also has significant anti-Parkinsons potential. Still, I'm sure I can safely say that none of us want to be medicated or repeatedly dosed every time we take a bite.

TBHQ is a hard chemical to dislike since it has numerous therapeutic potentials. So let's support the continued independent investigations into the antioxidant and other potentials of TBHQ while we refuse to eat food that contains it. If we had the cooperation of the masses then TBHQ wouldn't be used in food. If we simply boycotted the foods it was used in it wouldn't be used. If we don't buy something they stop making it and as more of us opt for a clean diet maybe we can get closer to a chemical-free food supply. Don't buy Fast Food until it's chemical-free and eat whole foods, fresh fruits, vegetables, nuts, seeds, berries, legumes, herbs, meats, fish and dairy.

“These data indicate that tBHQ-exacerbated stroke damage might be due to the compromised Blood Brain Barrier permeability in permanent stroke.”

Neurotoxicology And Teratology • January 2016

Tert-butylhydroquinone compromises survival in murine experimental stroke

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Abstract

Tert-butylhydroquinone (tBHQ), an Nrf2 signaling pathway inducer that is widely used as a food additive in the U.S., prevents oxidative stress-induced cytotoxicity in neurons. This study assesses the effects of tBHQ on ischemic stroke outcomes in mice. We measured infarct size, neurological deficits, and brain volume after tBHQ treatments in murine permanent middle cerebral artery occlusion (pMCAO) model in vivo. Further, we evaluated the regulation of tBHQ on mitochondrial function in cerebrovascular endothelial cells in vitro, which is critical to the blood-brain barrier (BBB) permeability. Our results demonstrated that tBHQ increased post-stroke mortality and worsened stroke outcomes. Mitochondrial function was suppressed by tBHQ treatment of cerebrovascular endothelial cells, and this suppression was potentiated by co-treatment with lipopolysaccharide (LPS), the bacterial mimic. These data indicate that tBHQ-exacerbated stroke damage might be due to the compromised BBB permeability in permanent stroke.

http://www.ncbi.nlm.nih.gov/pubmed/26827673

“... t-BHQ can protect against lead neurotoxicity.”

Oxidative Medicine And Cellular Longevity • January 2016

t-BHQ Provides Protection against Lead Neurotoxicity via Nrf2/HO-1 Pathway

Author information
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Abstract

The neurotoxicity of lead has been well established, and oxidative stress is strongly associated with lead-induced neurotoxicity. Nrf2 is important for protection against oxidative stress in many disease models. We applied t-BHQ, which is an Nrf2 activator, to investigate the possible role of Nrf2 in the protection against lead neurotoxicity. t-BHQ significantly attenuated the oxidative stress in developmental rats by decreasing MDA level, as well as by increasing SOD activity and GSH content, in the hippocampus and frontal cortex. Furthermore, neuronal apoptosis was detected by Nissl staining, and Bax expression was inhibited in the t-BHQ-treated group. Results showed that t-BHQ suppressed ROS production and caspase 3/7 activity but increased intracellular GSH content, in SH-SY5Y cells under lead exposure. Moreover, in vivo and in vitro, t-BHQ enhanced the nuclear translocation of Nrf2 and binding to ARE areas but did not induce Nrf2 transcription. These phenomena were confirmed using RT-PCR, EMSA, Western blot, and immunofluorescence analyses. Subsequent upregulation of the expression of HO-1, NQO1, and GCLC was observed. However, knockdown of Nrf2 or HO-1 adversely affected the protective effects of t-BHQ against lead toxicity in SH-SY5Y cells. Thus, t-BHQ can protect against lead neurotoxicity, depending on the Nrf2/HO-1 pathway.

Full Text, Graphs, Charts and 52 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4698940/

“tert-Butylhydroquinone (BHQ), an antioxidant used as a food additive, exhibits an anticancer effect at low doses, but is carcinogenic in rodents at high doses.”

Chemical And Biological Interactions • June 2015

Protective roles of aldo-keto reductase 1B10 and autophagy against toxicity induced by p-quinone metabolites of tert-butylhydroquinone in lung cancer A549 cells

Author information
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Abstract

tert-Butylhydroquinone (BHQ), an antioxidant used as a food additive, exhibits an anticancer effect at low doses, but is carcinogenic in rodents at high doses. BHQ is metabolized into cytotoxic tert-butylquinone (TBQ), which is further converted to 6-tert-butyl-2,3-epoxy-4-hydroxy-5-cyclohexen-1-one (TBEH) through 6-tert-butyl-2,3-epoxy-4-benzoquinone (TBE). Both TBQ and TBE are cytotoxic, but their toxic mechanisms have not been fully characterized. In this study, we have investigated the toxic mechanisms of TBQ and TBE, and the defense system against the two p-quinones using lung cancer A549 cells. TBQ and TBE, but not BHQ and TBEH, showed cytotoxicity to A549 cells. Neither caspase-3 activation nor an increase in the expression of endoplasmic reticulum stress-associating target genes was observed. TBQ and TBE reacted with reduced glutathione, and significantly decreased the glutathione level in A549 cells, suggesting that the cytotoxicity of the p-quinones is caused by their high electrophilicity reacting with biomolecules. The A549 cells treated with the p-quinones also showed increased levels of autophagic vacuoles and LC3-II protein, which are specific autophagy markers. An autophagy inhibitor, 3-methyladenine (3MA), decreased the LC3-II production by the p-quinones, but enhanced the cytotoxicity induced by TBQ and TBE, suggesting that autophagy contributes to alleviating the p-quinone-triggered cytotoxicity. In addition, the TBE-induced cytotoxicity and autophagy activation in the cells were significantly suppressed by overexpression of aldo-keto reductase (AKR)1B10 that efficiently reduces TBE into TBEH, and were augmented by pretreatment with a potent AKR1B10 inhibitor, C1. The effects of 3MA and C1 on the TBE-induced cytotoxicity were additive. The data provides evidence for the first time that autophagy and AKR1B10 contribute to the defense system against the cytotoxicity caused by the electrophilic p-quinone metabolites of BHQ.

http://www.ncbi.nlm.nih.gov/pubmed/25289770

“Tert-butylhydroquinone (TBHQ) is an antioxidant compound which shows multiple cytoprotective actions. We suggest that TBHQ treatment may represent a novel strategy for timely activation of the cytoprotective Akt pathway in stressed myocardium.”

Science Reports • August 2015

The antioxidant compound tert-butylhydroquinone activates Akt in myocardium, suppresses apoptosis and ameliorates pressure overload-induced cardiac dysfunction

Author information

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Abstract

Tert-butylhydroquinone (TBHQ) is an antioxidant compound which shows multiple cytoprotective actions. We evaluated the effects of TBHQ on pathological cardiac remodeling and dysfunction induced by chronic overload. Pressure overload was created by transverse aortic constriction (TAC) in male C57BL/6 mice. TBHQ was incorporated in the diet and administered for 4 weeks. TBHQ treatment prevented left ventricular dilatation and cardiac dysfunction induced by TAC, and decreased the prevalence of myocardial apoptosis. The beneficial effects of TBHQ were associated with an increase in Akt activation, but not related to activations of Nrf2 or AMP-activated protein kinase. TBHQ-induced Akt activation was accompanied by increased phosphorylation of Bad, glycogen synthase kinase-3ß (GSK-3ß) and mammalian target of rapamycin (mTOR). Mechanistically, we showed that in cultured H9c2 cells and primary cardiac myocytes, TBHQ stimulated Akt phosphorylation and suppressed oxidant-induced apoptosis; this effect was abolished by wortmannin or an Akt inhibitor. Blockade of the Akt pathway in vivo accelerated cardiac dysfunction, and abrogated the protective effects of TBHQ. TBHQ also reduced the reactive aldehyde production and protein carbonylation in stressed myocardium. We suggest that TBHQ treatment may represent a novel strategy for timely activation of the cytoprotective Akt pathway in stressed myocardium.

Full Text, Graphs, Charts and 65 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4531315/

“The neurotoxicity of fluoride is associated with oxidative stress ...
The present study aimed to investigate the possible neuroprotective role of tert-butylhydroquinone (tBHQ).
These findings indicated that tBHQ pretreatment conferred protective effect on PC12 cells
against odium fluoride-induced apoptotic cell death and oxidation-redox imbalance ...”

Cellular And Molecular Neurobiology • October 2015

Protective Role of tert-Butylhydroquinone Against Sodium Fluoride-Induced Oxidative Stress and Apoptosis in PC12 Cells

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Abstract

The neurotoxicity of fluoride is associated with oxidative stress due to imbalance between production and removal of reactive oxygen species (ROS). In contrast, induction of detoxifying and antioxidant genes through activation of NF-E2-related factor 2 (Nrf2) has been implicated in preventing oxidative stress and apoptosis in neurodegenerative diseases. The present study aimed to investigate the possible neuroprotective role of tert-butylhydroquinone (tBHQ), a general Nrf2 activator, on sodium fluoride (NaF)-induced oxidation damage and apoptosis in neuron-like rat pheochromocytoma (PC12) cells. Pretreatment with tBHQ protected PC12 cells against NaF-induced cytotoxicity as measured by MTT assay and apoptosis detection, simultaneously, inhibited NaF-induced overproduction of intracellular ROS and reduction of total glutathione content. Furthermore, NaF or tBHQ induced the stabilization of Nrf2, and enhanced expression of heme oxygenase-1 (HO-1) and y-glutamylcysteine synthetase (y-GCS) as a consequence of Nrf2 inducing. These findings indicated that tBHQ pretreatment conferred protective effect on PC12 cells against NaF-induced apoptotic cell death and oxidation-redox imbalance through stabilization of Nrf2 and elevation of downstream HO-1 and y-GCS expressions.

http://www.ncbi.nlm.nih.gov/pubmed/25911493

“The results showed that ... tBHQ markedly decreased ... inflammatory cytokines production in the injured spinal cord. Administration of tBHQ also significantly attenuated Spinal Cord Injury induced hindlimb locomotion deficits, spinal cord edema, and apoptosis. To conclude, pre-treatment with tBHQ could attenuate the spinal cord inflammatory response after Spinal Cord Injury.”

Annals In Clinical Laboratory Science • Spring 2014

Tert-butylhydroquinone protects the spinal cord against inflammatory response produced by spinal cord injury

Author information

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Abstract

Antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) has been shown in our previous studies to play an important role in protection against spinal cord injury (SCI) induced inflammatory response. The objective of this study was to test whether tert-butylhydroquinone (tBHQ), a novel Nrf2 activator, can protect the spinal cord against SCI-induced inflammatory damage. Adult male Sprague-Dawley rats were subjected to laminectomy at T8-T9 and compression with a vascular clip. Three groups were analyzed: a sham group, a SCI group, and a SCI+rhEPO group (n=16 per group). We measured Nrf2 and nuclear factor kappa B (NF-κB) binding activities by an electrophoretic mobility shift assay (EMSA). We also measured the concentrations of tumor necrosis factor-*a* (TNF-*a*), interleukin-1ß (IL-1ß), and interleukin-6 (IL-6) by an enzyme-linked immunosorbent assay (ELISA); we also measured hindlimb locomotion function by the Basso, Beattie, and Bresnahan (BBB) rating, spinal cord edema by wet/dry weight method, and apoptosis by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) analysis. The results showed that the induction of the Nrf2 activity by tBHQ markedly decreased NF-κB activation and inflammatory cytokines production in the injured spinal cord. Administration of tBHQ also significantly attenuated SCI induced hindlimb locomotion deficits, spinal cord edema, and apoptosis. To conclude, pre-treatment with tBHQ could attenuate the spinal cord inflammatory response after SCI.

http://www.ncbi.nlm.nih.gov/pubmed/24795053

“Tert-butylhydroquinone (tBHQ), an Nrf2 activator, has demonstrated neuroprotection against brain trauma and ischemic stroke in vivo ... the administration of tBHQ abated the development of early brain injury and cognitive dysfunction in this subarachnoid hemorrhage model.”

PLoS One • May 2014

Tert-butylhydroquinone alleviates early brain injury and cognitive dysfunction after experimental subarachnoid hemorrhage: role of Keap1/Nrf2/ARE pathway

Author information
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Abstract

Tert-butylhydroquinone (tBHQ), an Nrf2 activator, has demonstrated neuroprotection against brain trauma and ischemic stroke in vivo. However, little work has been done with respect to its effect on early brain injury (EBI) after subarachnoid hemorrhage (SAH). At the same time, as an oral medication, it may have extensive clinical applications for the treatment of SAH-induced cognitive dysfunction. This study was undertaken to evaluate the influence of tBHQ on EBI, secondary deficits of learning and memory, and the Keap1/Nrf2/ARE pathway in a rat SAH model. SD rats were divided into four groups: (1) Control group (n=40); (2) SAH group (n=40); (3) SAH+vehicle group (n=40); and (4) SAH+tBHQ group (n=40). All SAH animals were subjected to injection of autologous blood into the prechiasmatic cistern once in 20 s. In SAH+tBHQ group, tBHQ was administered via oral gavage at a dose of 12.5 mg/kg at 2 h, 12 h, 24 h, and 36 h after SAH. In the first set of experiments, brain samples were extracted and evaluated 48 h after SAH. In the second set of experiments, changes in cognition and memory were investigated in a Morris water maze. Results shows that administration of tBHQ after SAH significantly ameliorated EBI-related problems, such as brain edema, blood-brain barrier (BBB) impairment, clinical behavior deficits, cortical apoptosis, and neurodegeneration. Learning deficits induced by SAH was markedly alleviated after tBHQ therapy. Treatment with tBHQ markedly up-regulated the expression of Keap1, Nrf2, HO-1, NQO1, and GSTß1 after SAH. In conclusion, the administration of tBHQ abated the development of EBI and cognitive dysfunction in this SAH model. Its action was probably mediated by activation of the Keap1/Nrf2/ARE pathway.

Full Text with Charts, Graphs and 28 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4029824/

Journal Of Surgical Research • May 2014

Pretreatment with tert-butylhydroquinone attenuates cerebral oxidative stress in mice after traumatic brain injury

Author information

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Abstract

BACKGROUND

Traumatic brain injury (TBI) is a worldwide health problem, identified as a major cause of death and disability. Increasing evidence has shown that oxidative stress plays an important role in TBI pathogenesis. The antioxidant transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), is a known mediator in protection against TBI-induced brain damage. The objective of this study was to test whether tert-butylhydroquinone (tBHQ), a novel Nrf2 activator, can protect against TBI-induced oxidative stress.

METHODS

Adult male imprinting control region mice were randomly divided into three groups: (1) sham + vehicle group; (2) TBI + vehicle group; and (3) TBI + tBHQ group. Closed-head brain injury was applied using
the Feeney weight-drop method. We accessed the neurologic outcome of mice at 24 h after TBI, and subsequently measured protein levels of Nrf2 and the NOX2 subunit of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), the concentration of malondialdehyde, superoxide dismutase activity, and brain edema.

RESULT

The NOX2 protein level was increased fivefold in the TBI + vehicle group, whereas pretreatment with tBHQ markedly attenuated the NOX2 protein expression relative to that in the TBI + vehicle group. TBI increased Nrf2 formation by 5% compared with the sham group, whereas treatment with tBHQ further upregulated the Nrf2 protein level by 12% compared with the sham group. The level of the oxidative damage marker malondialdehyde was reduced by 29% in the TBI + tBHQ group compared with the TBI + vehicle group, Moreover, pretreatment with tBHQ significantly increased the antioxidant enzyme superoxide dismutase activity. Administration of tBHQ also significantly decreased TBI-induced brain edema and neurologic deficits.

CONCLUSIONS

Pretreatment with tBHQ effectively attenuated markers of cerebral oxidative stress after TBI, thus supporting the testing of tBHQ as a potential neuroprotectant and adjunct therapy for TBI patients.

http://www.ncbi.nlm.nih.gov/pubmed/24387843

“morphology of DAPI stained cells and DNA fragmentation assay using gel electrophoresis showed clear fragmentation in the chromatin and DNA rings within the nucleus of cell’s treated TBHQ.”

Food Chemistry • June 2014

Cytotoxicity and DNA damage properties of tert-butylhydroquinone (TBHQ) food additive

Author information

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Abstract

Tert-butylhydroquinone (TBHQ) was tested for potential cytotoxicity and genotoxicity upon A549 lung cancer cells and Human Umbilical Vein Endothelial Cells (HUVEC). Cytotoxicity was evaluated by MTT assay and flow cytometry analysis, while genotoxicity was assessed in vitro by alkaline comet, DNA fragmentation and DAPI staining assays. TBHQ dose- and time-dependently decreased the growth of A549 and HUVEC cells. Flow cytometry analyses determined early and late apoptosis in the treated cells. Also, single strand DNA breaking has been observed through comet assay technique. In addition, morphology of DAPI stained cells and DNA fragmentation assay using gel electrophoresis showed clear fragmentation in the chromatin and DNA rings within the nucleus of cell’s treated TBHQ.

http://www.ncbi.nlm.nih.gov/pubmed/24491735

DAPI

DAPI (4′,6-diamidino-2-phenylindole) is a fluorescent stain that binds strongly to A-T rich regions in DNA. It is used extensively in fluorescence microscopy. As DAPI can pass through an intact cell membrane, it can be used to stain both live and fixed cells, though it passes through the membrane less efficiently in live cells and therefore the effectiveness of the stain is lower. DAPI can be used for fixed cell staining. The concentration of DAPI needed for live cell staining is generally very high; it is rarely used for live cells. It is labeled non-toxic in its MSDS, incorrectly, and though it was not shown to have mutagenicity to E. coli, it is labelled as a known mutagen in manufacturer information. As it is a DNA binding compound, it is likely to have some low level mutagenic properties and care should be taken in its handling and disposal.

“Genes induced by tBHQ in 4-dpf zebrafish included those involved in glutathione synthesis and utilization, signal transduction, and DNA damage/stress response.”

PLoS One • November 2014

The transcriptional response to oxidative stress during vertebrate development: effects of tert-butylhydroquinone and 2,3,7,8-tetrachlorodibenzo-p-dioxin

Author information

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Abstract

Oxidative stress is an important mechanism of chemical toxicity, contributing to teratogenesis and to cardiovascular and neurodegenerative diseases. Developing animals may be especially sensitive to chemicals causing oxidative stress. The developmental expression and inducibility of anti-oxidant defenses through activation of NF-E2-related factor 2 (NRF2) affect susceptibility to oxidants, but the embryonic response to oxidants is not well understood. To assess the response to chemically mediated oxidative stress and how it may vary during development, zebrafish embryos, eleutheroembryos, or larvae at 1, 2, 3, 4, 5, and 6 days post fertilization (dpf) were exposed to DMSO (0.1%), tert-butylhydroquinone (tBHQ; 10 μM) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; 2 nM) for 6 hr. Transcript abundance was assessed by real-time qRT-PCR and microarray. qRT-PCR showed strong (4- to 5-fold) induction of gstp1 by tBHQ as early as 1 dpf. tBHQ also induced gclc (2 dpf), but not sod1, nqo1, or cyp1a. TCDD induced cyp1a but none of the other genes. Microarray analysis showed that 1477 probes were significantly different among the DMSO-, tBHQ-, and TCDD-treated eleutheroembryos at 4 dpf. There was substantial overlap between genes induced in developing zebrafish and a set of marker genes induced by oxidative stress in mammals. Genes induced by tBHQ in 4-dpf zebrafish included those involved in glutathione synthesis and utilization, signal transduction, and DNA damage/stress response. The strong induction of hsp70 determined by microarray was confirmed by qRT-PCR and by use of transgenic zebrafish expressing enhanced green fluorescent protein (EGFP) under control of the hsp70 promoter. Genes strongly down-regulated by tBHQ included mitfa, providing a molecular explanation for the loss of pigmentation in tBHQ-exposed embryos. These data show that zebrafish embryos are responsive to oxidative stress as early as 1 dpf, that responsiveness varies with development in a gene-specific manner, and that the oxidative stress response is substantially conserved in vertebrate animals.

Full text, Graphs, Charts and 137 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4234671/

Journal Of Antimicrobial Chemotherapy • June 2013

Antibacterial activity and mode of action of tert-butylhydroquinone (TBHQ) and its oxidation product, tert-butylbenzoquinone (TBBQ)

Author information

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Abstract

OBJECTIVES

The antioxidant tert-butylhydroquinone (TBHQ) is a food additive reported to have antibacterial activity, and may therefore have application in the healthcare setting. This study sought to characterize the antibacterial activity and mode of action of TBHQ and its oxidation product, tert-butylbenzoquinone (TBBQ).

METHODS

The stability of TBHQ/TBBQ was studied in buffer. Susceptibility testing was performed by broth microdilution, and killing and lytic activity were evaluated by viable counting and culture turbidity measurements. Mode of action studies included following the incorporation of radiolabelled precursors into macromolecules. The effect of TBHQ/TBBQ upon bacterial and mammalian membranes was assessed using the BacLight(TM) assay and by monitoring the haemolysis of equine erythrocytes.

RESULTS

TBHQ underwent oxidation in solution to form TBBQ. When oxidation was prevented, TBHQ lacked useful antibacterial activity, indicating that TBBQ is responsible for the antibacterial activity attributed to TBHQ. TBBQ demonstrated activity against Staphylococcus aureus SH1000 (MIC 8 mg/L) and against a panel of clinical S. aureus isolates (MIC90 16 mg/L). TBBQ at 4× MIC caused a >4 log10 drop in cell viability within 6 h without lysis, and eradicated staphylococcal biofilms at 8× MIC. TBBQ did not display preferential inhibition of any single macromolecular synthetic pathway, but caused loss of staphylococcal membrane integrity without haemolytic activity.

CONCLUSIONS

TBBQ is responsible for the antibacterial activity previously ascribed to TBHQ. TBBQ prompts loss of staphylococcal membrane integrity; it is rapidly and extensively bactericidal, but is non-lytic. In view of the potent and selective bactericidal activity of TBBQ, this compound warrants further investigation as a candidate antistaphylococcal agent.

Full Text with Graphs, Charts and 32 References

http://www.jac.oxfordjournals.org/content/68/6/1297.long

“These results indicate that tBHQ suppresses body weight gain in mice ...”

Archives In Pharmacological Research • July 2013

Tert-butylhydroquinone reduces lipid accumulation in C57BL/6 mice with lower body weight gain

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Abstract

tert-Butylhydroquinone (tBHQ) is a commonly used antioxidant additive that is approved for human use by both the Food and Agriculture Organization and the World Health Organization (FAO/WHO). In this study, we examined the effect of tBHQ on body weight gain and found that food supplementation with 0.001 % (w/w) tBHQ inhibited 61.4 % ($P < 0.01$) of body weight gain in high-fat diet (HFD)-induced C57BL/6 mice, and the oral administration of tBHQ (1.5 mg/kg) reduced 47.5 % ($P < 0.05$) of body weight gain in normal diet fed db/db mice. The HFD increased lipid deposit in adipocytes, but these were reduced significantly by tBHQ treatment in C57BL/6 mice. tBHQ supplementation significantly lowered the plasma triglyceride and total cholesterol, with reduced size of accumulated fat mass. The rate limiting enzyme of beta-oxidation (ACOX1) was significantly over-expressed in the liver with tBHQ treatment. These results indicate that tBHQ suppresses body weight gain in mice, possibly at least related to the up-regulation of ACOX1 gene expression.

http://www.ncbi.nlm.nih.gov/pubmed/23585332

“At high concentrations, tert-butylhydroquinone (tBHQ), a phenolic antioxidant frequently used as a food preservative, exerts cytotoxic effects ...”

Archives In Toxicology • September 2012

Paradoxical cytotoxicity of tert-butylhydroquinone in vitro: What kills the untreated cells?

Author information

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Abstract

At high concentrations, tert-butylhydroquinone (tBHQ), a phenolic antioxidant frequently used as a food preservative, exerts cytotoxic effects, which are closely linked to its ability to form reactive oxygen species as a consequence of redox cycling processes. Here we describe that treatment of murine 3T3 cells with 300 µg/ml of tBHQ in 96-well culture plates induces the death of untreated cells in neighboring wells on the same plate. The mechanisms underlying that effect were investigated. Death of the seemingly untreated neighboring cells was caused by the more toxic and volatile tBHQ oxidation product tert-butyl-p-benzoquinone (tBQ) present at up to 3 µg/ml in the untreated neighboring wells. tBQ was formed from tBHQ in a non-enzymatic process involving copper ions and oxygen. The unexpected perturbation of cytotoxicity testing following treatment with tBHQ by its volatile metabolite tBQ shows that not only metabolic processes but also non-enzymatic mechanisms have to be considered as important parameters for in vitro assays. Furthermore, our data show that even cells several wells away from the treated wells do not necessarily constitute proper “untreated” controls when cells are treated with the frequently used compound tBHQ. This might lead to an underestimation of the effects observed on the Nrf2 signaling pathway, where tBHQ is frequently used as an inductor in vitro.

http://www.ncbi.nlm.nih.gov/pubmed/22466069

“These results indicate that t-BHQ exhibits strong cytotoxicity against MDCK cells ...”

Journal Of Veterinary Medicine And Science • May 2012

Effects of oxidative stress caused by tert-butylhydroquinone on cytotoxicity in MDCK cells

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Abstract

Antioxidant and oxidative stress effects of prooxidants are generally dose-dependent, and these effects depend on the prooxidant species and cell type. However, the cellular response to oxidant challenge is a complicated interplay of events involving cellular expression of phase II detoxification enzymes and cellular metal metabolism. This study demonstrates the effect of tert-butylhydroquinone (t-BHQ)-induced oxidative stress on MDCK cells. Cell toxicity tests were carried out using the crystal violet (CV) assay with the following prooxidants: t-BHQ, diethyl maleate (DEM), hydrogen peroxide (H(2)O(2)), diquat (DQ) and ß-naphthoflavone (ß-NF). Except for ß-NF, these prooxidants showed dose-dependent cytotoxicity besides the most potent t-BHQ cytotoxicity. Only t-BHQ and DEM caused significant time-dependent expression of ferritin protein as an antioxidant, which segregates Fe(2+), causing the Fenton reaction. t-BHQ and DEM increased formation of lipid peroxidation, but DQ showed a tendency to decrease lipid peroxidation levels. In XTT assay, even when substantial cell death was observed in the CV assay, t-BHQ appeared to increase cell viability by enhancing XTT reduction, likely through the production of NADPH. Although curcumin, which induces cytoprotective phase II enzymes and chelates metal irons, decreased cell viability, it inhibited t-BHQ cytotoxicity. These results indicate that t-BHQ exhibits strong cytotoxicity against MDCK cells, an effect mitigated by curcumin, and that t-BHQ-induced oxidative stress activates the pentose phosphate pathway.

MDCK CELLS

MDCK Cells are derived from canine kidney and the MDCK cell line—also known as NBL-2 or ATCC® CCL-34™—this patented cell line has been used since 1958 to produce the influenza vaccine and other vaccines and in immunology related experiments where viable and rapidly reproducing cells are required.

Full Text PDF with Graphs, Charts and 34 References

https://www.jstage.jst.go.jp/article/jvms/74/5/74_11-0412/_pdf

“... pretreatment with tBHQ conferred neuro-protection against paraquat-induced Parkinsonism ...”

Archives In Toxicology • November 2012

Neuroprotective effects of tert-butylhydroquinone on paraquat-induced dopaminergic cell degeneration in C57BL/6 mice and in PC12 cells

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Abstract

The present study was aimed at determining the role of paraquat (PQ) in the activation of the NF-E2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) pathway and the possible neuroprotective effects of tert-butylhydroquinone (tBHQ) pretreatment on PQ-induced neurodegeneration in vivo and in vitro. 7 mg/kg PQ treatment of male C57BL/6 mice caused decreased spontaneous locomotor activity, decreased tyrosine hydroxylase (TH)-positive neurons, increased terminal deoxynucleotidyl transferase-mediated dUTP biotin nick end-labeling (TUNEL)-positive cells in the substantia nigra, as well as increased protein levels of both nuclear Nrf2 and HO-1. In PQ-treated mice, pretreatment with 1 % tBHQ (w/w) significantly attenuated impairments in behavioral performance, decreased TH-positive neurons, and increased TUNEL-positive cells in the substantia nigra, as well as increased protein expression of both nuclear Nrf2 and HO-1. Pretreatment with 40 μM tBHQ protected PC12 cells against 100 and 300 μM PQ-mediated cytotoxicity. The dual-luciferase reporter gene also revealed that the transcriptional activation of HO-1 gene expression of the antioxidant responsive element via Nrf2 occurred as a consequence of 100 and 300 μM PQ exposure. Collectively, these results clearly indicated for the first time that the Nrf2/HO-1 pathway in the substantia nigra was activated by PQ, and pretreatment with tBHQ conferred neuroprotection against PQ-induced Parkinsonism presumably by increasing Nrf2 and HO-1 expression.

http://www.ncbi.nlm.nih.gov/pubmed/22983789

“Collectively, our data suggest that TBHQ may have therapeutic potential for Alzheimer’s disease by increasing brain antioxidant capacity/reducing oxidative stress level and by stimulating Aß (beta) degradation/clearance pathways.”

Journal Of Alzheimer’s Disease • December 2011

Therapeutic potential and anti-amyloidosis mechanisms of tert-butylhydroquinone for Alzheimer’s disease

Author information

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Abstract

Alzheimer’s disease (AD) is a major cause of dementia in the elderly with no effective treatment. Accumulation of amyloid-ß peptide (Aß) in the brain, one of the pathological features of AD, is considered to be a central disease-causing and disease-promoting event in AD. In this study, we showed that feeding male AßPP/PS1 transgenic mice, a well established mouse model of AD, with a diet containing phenolic antioxidant tert-butylhydroquinone (TBHQ) dramatically reduced brain Aß load with no significant effect on the amounts of alpha- and beta-C-terminal fragments or full-length AßPP. Further studies showed that TBHQ diet inhibited the expression of plasminogen activator inhibitor-1 (PAI-1), a protease inhibitor which plays a critical role in brain Aß accumulation in AD, accompanied by increases in the activities of tissue type and urokinase type plasminogen activators (tPA and uPA) as well as plasmin. Moreover, we showed that TBHQ diet increased the expression of low density lipoprotein related protein-1, a multi ligand endocytotic receptor involved in transporting Aß out of the brain, and plasma Aß(40) and Aß(42) levels. We also showed that TBHQ diet increased the concentration of glutathione, an important antioxidant, and suppressed the expression of NADPH oxidase 2 as well as lipid peroxidation. Collectively, our data suggest that TBHQ may have therapeutic potential for AD by increasing brain antioxidant capacity/reducing oxidative stress level and by stimulating Aß degradation/clearance pathways.

Full Text, Graphs, Charts and 64 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3686822/

“The results of the present study suggest that tBHQ administration could suppress the intestinal inflammation and reduce the mucosal damage following Traumatic Brain Injury.”

Mediators Of Inflammation • January 2010

Effects of tert-butylhydroquinone on intestinal inflammatory response and apoptosis following traumatic brain injury in mice

Author information

Jin W1, Ni H, Dai Y, Wang H, Lu T, Wu J, Jiang J, Liang W.

Abstract

Traumatic brain injury (TBI) can induce intestinal inflammatory response and mucosal injury. Antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) has been shown in our previous studies to prevent oxidative stress and inflammatory response in gut after TBI. The objective of this study was to test whether tert-butylhydroquinone (tBHQ), an Nrf2 inducer, can protect against TBI-induced intestinal inflammatory response and mucosal injury in mice. Adult male ICR mice were randomly divided into three groups: (1) sham + vehicle group, (2) TBI + vehicle group, and (3) TBI + tBHQ group (n = 12 per group). Closed head injury was adopted using Hall’s weight-dropping method. Intestinal mucosa apoptosis and inflammatory-related factors, such as nuclear factor kappa B (NF-κB), tumor necrosis factor-ß (TNF-ß), interleukin-1ß (IL-1ß), interleukin-6 (IL-6) and intercellular adhesion molecule-1 (ICAM-1), were investigated at 24 h after TBI. As a result, we found that oral treatment with 1% tBHQ prior to TBI for one week markedly decreased NF-κB activation, inflammatory cytokines production, and ICAM-1 expression in the gut. Administration of tBHQ also significantly attenuated TBI-induced intestinal mucosal apoptosis. The results of the present study suggest that tBHQ administration could suppress the intestinal inflammation and reduce the mucosal damage following TBI.

Full Text, Graphs, Charts and 38 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025385/

“Tert-butylhydroquinone induces mitochondrial oxidative stress ...”

Cellular Biology And Toxicology • December 2010

Tert-butylhydroquinone induces mitochondrial oxidative stress causing Nrf2 activation

Author information

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Abstract

Tert-butylhydroquinone (tBHQ), the major metabolite of butylated hydroxyanisole (BHA), induces an antioxidant response through the redox-sensitive transcription factor, nuclear factor-E2-related factor-2 (Nrf2). However, the mechanism by which tBHQ induces Nrf2 activity is not entirely understood. Here, we show that tBHQ preferentially alters the redox status in the mitochondrial compartment in HeLa cells. HeLa cells treated with tBHQ showed a preferential oxidation of mitochondrial thioredoxin-2 (Trx2), while cellular glutathione and cytosolic thioredoxin-1 were not affected. Preferential mitochondrial oxidation by tBHQ was supported by detection of reactive oxygen species (ROS) specific to this compartment. To determine the role of Trx2 in regulating downstream effects of tBHQ, HeLa cells were transiently transfected with an empty, Trx2, or C93S (Cys93Ser) Trx2 dominant-negative mutant expression vector. Overexpression of Trx2 decreased basal mitochondrial ROS production, whereas expression of C93S Trx2 enhanced it. In addition, under untreated conditions, expression of C93S Trx2 led to an increase in the basal activities of Nrf2. With tBHQ treatments, Trx2 overexpression suppressed Nrf2 accumulation and activity, whereas expression of C93S Trx2 had no effect on the degree of inducibility or Nrf2 accumulation but did increase the overall activity of Nrf2. Quantitative polymerase chain reaction analysis of Nrf2-regulated gene expression corroborate Trx2 control of tBHQ-mediated Nrf2 activation. These data show a compartment-specific effect where tBHQ-induced Nrf2 signaling is mediated by Trx2 and suggest that antioxidant status in various compartments would provide different levels of control of redox signaling.

http://www.ncbi.nlm.nih.gov/pubmed/20429028

CHAPTER FIVE

The Polysorbates • Excipients, Surfactants & Emulsifiers

The Peer Review

Visual problems are the primary disorder that occurs with the use of polysorbate 80, although this ingredient is also associated with growth and reproductive toxicity, cancer, organ poisoning and neurological side effects, among a myriad of additional diseases and disorders.

Evidence based on animal test data also indicates that polysorbate 80 may promote genetic mutations.

Polysorbates are surfactants and emulsifiers that reduce a solvent's surface tension to enable other substances to easily dissolve and stay dissolved. These solubilizing agents are a common ingredient in cosmetics and beauty products, as well as an additive in many processed foods.

In 2006, studies performed in test tubes using mammalian cells revealed polysorbate 80's mutagenic effects. Another study indicated that intravenous administration of this substance into rats significantly altered the subjects' reproductive process. Published scientific literature also related polysorbate 80 to severe allergic reactions, which eventually resulted in fatality cases. Due to polysorbate 80's emulsifying properties, it is commonly used in conjunction with other active ingredients for efficient delivery of medications. When used in combination with glycerin for ophthalmic applications, polysorbate 80 can cause blurred vision, with mild stinging and burning sensation around the application site.

Polysorbate 80 is known to cause various side effects, including abdominal pain, breathing difficulties, chills, confusion, loose bowel movements, pus accumulation, dizziness, headaches, retching and weight gain. Other side effects include anxiety, convulsions, motor impairment and slow speech. Although infrequent, fever, sore throat, hives, pale skin and unexplained exhaustion may also occur.

Polysorbate is also known as Polyoxythylene Sorbitan Monostearate, Tween 80, Tween 65, Polyoxyethylene 20, Sorbitan Tristerate 65, Polysorbate 60, Polysorbate 40 and Polysorbate 20, E433, Alkest, Carnarcel and simply Tween. It's an emulsifier, thickener, and stabilizer created by adding a steric acid molecule to sorbitol. It's a waxy substance used in foods for many reasons such as an anti-foaming agent in beverages, to help chocolate coatings not taste greasy, and aid in absorption of fat soluble vitamins in supplements.

Polysorbate 80 is known to be commonly contaminated with 1,4 dioxane which is known and proven to cause cancer in animals. Polysorbate also contains the contaminant ethylene oxide which has a very high human hazard rating of 8/10. The hazard rating for 1,4 dioxane is 10/10 so Polysorbate, often contaminated in the manufacturing process, is a dangerous food additive regardless of what any chemical industry or government sponsored data may say. There is more than enough independent peer review to confirm that repeated consumption of polysorbates and other excipients leads to disease in the human species. Evidence clearly shows that excipients in all of their forms and by all of their names are multi-system toxic in human beings and should be avoided.

This was a difficult chapter to compile because the research on Polysorbates as they're used in food is thin. Polysorbates fall into a class of chemicals called excipients, surfactants and emulsifiers in the food industry and other excipients, surfactants and emulsifiers are included in this chapter.

An excipient carries or helps to carry another chemical; a surfactant reduces surface tension and in this case, where the human body is concerned, a surfactant can reduce cellular surface tension allowing the entry of foreign chemical molecules into the cell or allowing other foreign molecules to cross a variety of other human system barriers; and an emulsifier, for example, keeps the vanilla or chocolate flavoring mixed evenly through a gallon of your favorite vanilla or chocolate ice cream. These chemicals— excipients, surfactants and emulsifiers—are used in commercial manufacturing and a wide variety of industrial manufacturing, in almost all over-the-counter and prescription or injectable drugs, vitamins and supplements and in processed foods.

This class of food drugs may attenuate life-saving drugs you could be taking regularly or even temporarily, severely reducing their effects, they may attenuate organ system functions and cellular mechanisms and they may cause other system disruptions, various diseases and disorders when consumed in high amounts or even moderate but consistent amounts across decades. These chemicals are all food drugs. Novel excipients themselves can be patented and sometimes a particular formulation involving an excipient is kept as a trade secret in which case "natural flavor" or natural color" serves as sufficient cover to maintain an uninformed consuming population.

Excipients facilitate long-term stabilization, bulking up mixed formulations that contain potent active ingredients necessary in only very small amounts, so they act as "fillers", or "diluents", Sometimes excipients have a medical or therapeutic effect on the active ingredient in a food or drug like aiding in absorption or reducing the thickness or viscosity of a liquid preparation but they have no nutritional value.

Excipient - a substance that serves as the **vehicle or medium** for a drug or other active substance.

Surfactant - a substance that tends to **reduce the surface tension** of a liquid in which it is dissolved.

Emulsifier - a substance that **stabilizes** a mixture, in particular a food additive used to stabilize processed foods.

Attenuate - **reduce** the force, effect, or value of, reduce the amplitude of (a signal, drug or electric current).

“Immature neonates in a Brazilian Neonatal Intensive Care Unit are exposed to a variety of Off Label Use, Unlicensed Drugs and potentially harmful drugs and excipients.”

BMC Pediatrics • January 2016

Off-label use and harmful potential of drugs in a NICU in Brazil: A descriptive study

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Abstract

BACKGROUND

Neonates admitted to neonatal intensive care units (NICU) are exposed to a wide variety of drugs, most without any data on safety and efficacy.

OBJECTIVE

To describe the drugs prescribed to different groups of neonates hospitalized in a NICU, and to analyze off-label use and harmful potential of drugs, in terms of the potential risks.

METHODS

This was a six-month retrospective cohort study of drug use in a NICU, with neonates who were inpatients for a period of over 24 hours, and using prescription data from electronic medical records. Drug information found in the package leaflets, in the British National Formulary for Children 2012-2013, and in the Thomson Micromedex database were compared. Drugs and excipients considered potentially harmful were evaluated according to the literature.

RESULTS

One hundred ninety-two neonates were included in the study, with a mean gestational age (GA) of 33.3 weeks (SD±4.3), 75.0 % were preterm, with an average of 18.8 days of hospitalization (SD±18.1), and a total of 3617 neonates-day. 3290 prescriptions were registered, on average 17.1 prescriptions/neonate (SD±17.9) and 8.8 drugs/neonate (SD±5.9). The number of prescriptions and drugs was higher in neonates with GA <31 weeks ($p < 0.05$). Anti-infectives for systemic use, blood, alimentary tract and metabolism drug groups were more frequent, varying according to the GA. Neonates (99.5 %) were exposed to unlicensed drugs (UL) and off label use (OL), more frequently in GA <28 weeks ($p < 0.05$). Most OL drugs used were indicated for newborns. 15 potentially harmful drugs were used in more than 70 % of the neonates, and most were OL; exposure to harmful excipients occurred in 91.6 % of the neonates, a percentage even higher when considering immature neonates.

CONCLUSIONS

Immature neonates in a Brazilian NICU are exposed to a variety of OL, UL and potentially harmful drugs and excipients.

Full text, graphs, charts and 41 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4722776/

“Excipients of interest-free formulations are available for a substantial number of products currently used in European neonates. Replacement of only the most frequently used products may spare almost half of neonates from unnecessary exposure to excipients of interest.”

Paediatric Drugs • June 2016

Product Substitution as a Way Forward in Avoiding Potentially Harmful Excipients in Neonates

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Abstract

OBJECTIVES

Our objectives were to explore the possibility of avoiding neonatal exposure to potentially harmful excipients of interest (EOI)-parabens, polysorbate 80, propylene glycol, benzoates, saccharin sodium, sorbitol and ethanol-through product substitution in Europe.

METHODS

We performed a 3-day service evaluation survey and a 1-day point prevalence study in 20 and 21 European countries, respectively. Analysis included active pharmaceutical ingredients (APIs) used in ≥10 % of units. We calculated the potential reduction in number of products with EOI through substitution in three stages: (1) similar API and route of administration, (2) plus similar dosage form and (3) plus similar strength. The reduction of individual exposure was analysed according to the second-stage criteria.

RESULTS

We identified 137 products for 25 APIs that contained EOI. Substitution with EOI-free product(s) was available for 88 % (n = 120), 66 % (n = 91) and 31 % (n = 42) of products according to the first-, second- and third-stage criteria, respectively. Overall, 456 (63 % of 726) neonates received products containing EOI. Substitution of the products that had alternatives with similar API and dosage form would reduce the number of exposed neonates from 456 to 257 (44 % reduction).

CONCLUSIONS

EOI-free formulations are available for a substantial number of products currently used in European neonates. Replacement of only the most frequently used products may spare almost half of neonates from unnecessary exposure to EOI.

http://www.ncbi.nlm.nih.gov/pubmed/27099961

“These results support the emerging concept that perturbed host–microbiota interactions resulting in low-grade inflammation can promote adiposity and its associated metabolic effects. Moreover, they suggest that the broad use of emulsifying agents might be contributing to an increased societal incidence of obesity/metabolic syndrome and other chronic inflammatory diseases.”

Nature • February 2015

Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

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Abstract

The intestinal tract is inhabited by a large and diverse community of microbes collectively referred to as the gut microbiota. While the gut microbiota provides important benefits to its host, especially in metabolism and immune development, disturbance of the microbiota–host relationship is associated with numerous chronic inflammatory diseases, including inflammatory bowel disease and the group of obesity-associated diseases collectively referred to as metabolic syndrome. A primary means by which the intestine is protected from its microbiota is via multi-layered mucus structures that cover the intestinal surface, thereby allowing the vast majority of gut bacteria to be kept at a safe distance from epithelial cells that line the intestine1. Thus, agents that disrupt mucus–bacterial interactions might have the potential to promote diseases associated with gut inflammation. Consequently, it has been hypothesized that emulsifiers, detergent-like molecules that are a ubiquitous component of processed foods and that can increase bacterial translocation across epithelia in vitro2, might be promoting the increase in inflammatory bowel disease observed since the mid-twentieth century3. Here we report that, in mice, relatively low concentrations of two commonly used emulsifiers, namely carboxymethylcellulose and polysorbate-80, induced low-grade inflammation and obesity/metabolic syndrome in wild-type hosts and promoted robust colitis in mice predisposed to this disorder. Emulsifier-induced metabolic syndrome was associated with microbiota encroachment, altered species composition and increased pro-inflammatory potential. Use of germ-free mice and faecal transplants indicated that such changes in microbiota were necessary and sufficient for both low-grade inflammation and metabolic syndrome. These results support the emerging concept that perturbed host–microbiota interactions resulting in low-grade inflammation can promote adiposity and its associated metabolic effects. Moreover, they suggest that the broad use of emulsifying agents might be contributing to an increased societal incidence of obesity/metabolic syndrome and other chronic inflammatory diseases.

Full text, downloadable PDF, with Charts, Graphs and 45 references

http://www.nature.com/nature/journal/v519/n7541/full/nature14232.html#affil-auth

“Tween 80 enhanced ... the cytotoxicity of chlorfluazuron on Tn5B1-4 cells, and also improved a bit of the cytotoxicity of chlorpyrifos or tebufenozide on HepG2 cells.”

Environmental Toxicology And Pharmacology • March 2015

Synergistic effect of non-ionic surfactants Tween 80 and PEG6000 on cytotoxicity of insecticides

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Abstract

The use of surfactants in the development of a suitable formulation for insecticides should improve the solubility behavior, the permeability and the efficiency against pests meanwhile decrease the toxic risks of insecticides on human health. Cytotoxicity of insecticides including abamectin, chlorfluazuron, hexaflumuron, chlorpyrifos, and tebufenozide was assessed on human HepG2 and lepidopteran Tn5B1-4 cells utilizing insecticide alone and in combination with nontoxic concentrations of nonionic surfactants Tween 80 and PEG6000. The results showed avermection revealed high cytotoxicity, chlorfluazuron and hexaflumuron possessed median cytotoxicity, and chlorpyrifos and tebufenozide had little cytotoxicity on HepG2 and Tn5B1-4 cells. The co-incubation with Tween 80 and PEG6000 powerfully counteracted the cytotoxicity of avermectin. Tween 80 enhanced, whereas PEG6000 compressed, the cytotoxicity of chlorfluazuron on Tn5B1-4 cells, and also improved a bit of the cytotoxicity of chlorpyrifos or tebufenozide on HepG2 cells. PEG6000 was more suitable to be used as surfactant in improving insecticide solubility and reducing the cytotoxicity. The present investigation demonstrates the necessity of utilizing surfactants to weaken the cytotoxicity of insecticides.

http://www.ncbi.nlm.nih.gov/pubmed/25699500

“European neonates receive a number of potentially harmful pharmaceutical excipients.”

Abstract

OBJECTIVES

We aimed to describe administration of eight potentially harmful excipients of interest (EOI)-parabens, polysorbate 80, propylene glycol, benzoates, saccharin sodium, sorbitol, ethanol and benzalkonium chloride-to hospitalised neonates in Europe and to identify risk factors for exposure.

METHODS

All medicines administered to neonates during 1 day with individual prescription and demographic data were registered in a web-based point prevalence study. Excipients were identified from the Summaries of Product Characteristics. Determinants of EOI administration (geographical region, gestational age (GA), active pharmaceutical ingredient, unit level and hospital teaching status) were identified using multivariable logistical regression analysis.

RESULTS

Overall 89 neonatal units from 21 countries participated. Altogether 2095 prescriptions for 530 products administered to 726 neonates were recorded. EOI were found in 638 (31%) prescriptions and were administered to 456 (63%) neonates through a relatively small number of products (n=142; 27%). Parabens, found in 71 (13%) products administered to 313 (43%) neonates, were used most frequently. EOI administration varied by geographical region, GA and route of administration. Geographical region remained a significant determinant of the use of parabens, polysorbate 80, propylene glycol and saccharin sodium after adjustment for the potential covariates including anatomical therapeutic chemical class of the active ingredient.

CONCLUSIONS

European neonates receive a number of potentially harmful pharmaceutical excipients. Regional differences in EOI administration suggest that EOI-free products are available and provide the potential for substitution to avoid side effects of some excipients.

http://www.ncbi.nlm.nih.gov/pubmed/25854872

Archives Of Disease In Childhood • July 2015

Potentially harmful excipients in neonatal medicines: a pan-European observational study

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“Our results provide new insights into the toxicity evaluation of nanoparticles and our findings would help contribute to a better understanding of the neurotoxicity of biodegradable nanomaterials used in pharmaceutics.”

PLoS One • August 2015

Brain Localization and Neurotoxicity Evaluation of Polysorbate 80-Modified Chitosan Nanoparticles in Rats

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Abstract

The toxicity evaluation of inorganic nanoparticles has been reported by an increasing number of studies, but toxicity studies concerned with biodegradable nanoparticles, especially the neurotoxicity evaluation, are still limited. For example, the potential neurotoxicity of Polysorbate 80-modified chitosan nanoparticles (Tween 80-modified chitosan nanoparticles, TmCS-NPs), one of the most widely used brain targeting vehicles, remains unknown. In the present study, TmCS-NPs with a particle size of 240 nm were firstly prepared by ionic cross-linking of chitosan with tripolyphosphate. Then, these TmCS-NPs were demonstrated to be entered into the brain and specially deposited in the frontal cortex and cerebellum after systemic injection. Moreover, the concentration of TmCS-NPs in these two regions was found to decrease over time. Although no obvious changes were observed for oxidative stress in the in vivo rat model, the body weight was found to remarkably decreased in a dose-dependent manner after exposure to TmCS-NPs for seven days. Besides, apoptosis and necrosis of neurons, slight inflammatory response in the frontal cortex, and decrease of GFAP expression in the cerebellum were also detected in mouse injected with TmCS-NPs. This study is the first report on the sub-brain biodistribution and neurotoxicity studies of TmCS-NPs. Our results provide new insights into the toxicity evaluation of nanoparticles and our findings would help contribute to a better understanding of the neurotoxicity of biodegradable nanomaterials used in pharmaceutics.

Full text, photos, graphs, charts and 36 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4527829/

“Two-thirds of pharmaceutical preparations for neonates were used off-label. Newborns receive more auxiliary substances, which may be unsuitable for this age group and may even be toxic to them, via industrially manufactured pharmaceuticals.”

Journal Of Maternal, Fetal And Neonatal Medicine • September 2015

The prevalence and pattern of pharmaceutical and excipient exposure in a neonatal unit in Slovenia

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Abstract

OBJECTIVE

Because of the restraints on conducting studies on pharmaceutical use in sick newborns, many drugs are used off-label in this population. Moreover, industrially manufactured pharmaceuticals may contain different excipients, which may be either untested or not licensed for use in neonates. The aim of our study was to determine the prevalence and pattern of pharmaceutical and excipient exposure in newborns hospitalized at the Department of Neonatology, Ljubljana, Slovenia.

METHODS

A longitudinal prospective cross-sectional study was performed during a one-month period and included all hospitalized neonates. Route of administration, site of action, type of manufacture, licensing status, type and concentrations of excipients for all pharmaceuticals given to the neonates were determined.

RESULTS

Twenty seven different pharmaceutical preparations were prescribed to a total of 48 hospitalized newborns. In most cases, newborns were prescribed various pharmaceuticals that were not approved for use in this population. Newborns were exposed to 60 different excipients in industrially manufactured pharmaceutical preparations. More than half of the received pharmaceuticals contained potentially harmful and harmful excipients.

CONCLUSIONS

Two-thirds of pharmaceutical preparations for neonates were used off-label. Newborns receive more auxiliary substances, which may be unsuitable for this age group and may even be toxic to them, via industrially manufactured pharmaceuticals.

http://www.ncbi.nlm.nih.gov/pubmed/25316561

“Tween 20 and polyoxyl 35 castor oil may attenuate the human carboxylesterase activity; such inhibition should be taken into consideration during drug administration.”

PLoS One • April 2014

In vitro evaluation of the inhibitory potential of pharmaceutical excipients on human carboxylesterase 1A and 2

Author information

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Abstract

Two major forms of human carboxylesterase (CES), CES1A and CES2, dominate the pharmacokinetics of most prodrugs such as imidapril and irinotecan (CPT-11). Excipients, largely used as insert vehicles in formulation, have been recently reported to affect drug enzyme activity. The influence of excipients on the activity of CES remains undefined. In this study, the inhibitory effects of 25 excipients on the activities of CES1A1 and CES2 were evaluated. Imidapril and CPT-11 were used as substrates and cultured with liver microsomes in vitro. Imidapril hydrolase activities of recombinant CES1A1 and human liver microsomes (HLM) were strongly inhibited by sodium lauryl sulphate (SLS) and polyoxyl 40 hydrogenated castor oil (RH40) [Inhibition constant (Ki)=0.04 ± 0.01 μg/ml and 0.20 ± 0.09 μg/ml for CES1A1, and 0.12 ± 0.03 μg/ml and 0.76 ± 0.33 μg/ml, respectively, for HLM]. The enzyme hydrolase activity of recombinant CES2 was substantially inhibited by Tween 20 and polyoxyl 35 castor oil (EL35) (K(i) = 0.93 ± 0.36 μg/ml and 4.4 ± 1.24 μg/ml, respectively). Thus, these results demonstrate that surfactants such as SLS, RH40, Tween 20 and EL35 may attenuate the CES activity; such inhibition should be taken into consideration during drug administration.

Full text, graphs, charts and 46 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3974814/

“Polyoxyethylene hydrogenated castor oil 40 and polysorbate 80 reduce acute corneal toxicity and the antimicrobial effect of benzalkonium chloride. Possible interactions between benzalkonium chloride and other additives should be taken into consideration when evaluating the toxicity and antibacterial properties of benzalkonium chloride.”

Cornea • May 2014

Influence of different additives and their concentrations on corneal toxicity and antimicrobial effect of benzalkonium chloride

Author information

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Abstract

PURPOSE

The aim of this study was to examine the ophthalmic additives responsible for modulating acute corneal epithelial toxicity induced by benzalkonium chloride (BAC) and investigate the ability of polyoxyethylene hydrogenated castor oil 40 (HCO-40) and polysorbate 80 (PS-80) to reduce the corneal toxicity and antimicrobial effects of BAC.

METHODS

Cytotoxicity of the additives, which included glycerin, polyvinyl alcohol, propylene glycol, polyethylene glycol, and PS-80, on rabbit corneal epithelial cells was examined using the cell proliferation assay in the presence and absence of 0.02% BAC. The corneal transepithelial electrical resistance change after a 60-second exposure to HCO-40 or PS-80 mixed with 0.02% BAC was measured in living rabbits. Corneal damage was examined using scanning electron microscopy. The antimicrobial activities of HCO-40 and PS-80 with 0.02% BAC against Staphylococcus aureus, Propionibacterium acnes, Pseudomonas aeruginosa, Escherichia coli, and Streptococcus pneumoniae were assessed.

RESULTS

Of all the tested additives, only PS-80 could prevent the BAC-induced cytotoxicity. Corneal epithelial barrier function disorder caused by 0.02% BAC was significantly alleviated by either PS-80 or HCO-40 in a concentration-dependent manner. Scanning electron microscopy images showed an improvement of BAC-induced corneal epithelial toxicity after the addition of HCO-40 or PS-80. The antimicrobial effect of the BAC against P. aeruginosa, E. coli, and S. pneumoniae was reduced after adding HCO-40 or PS-80.

CONCLUSIONS

HCO-40 and PS-80 reduce acute corneal toxicity and the antimicrobial effect of BAC. Possible interactions between BAC and other additives should be taken into consideration when evaluating the toxicity and antibacterial properties of BAC.

http://www.ncbi.nlm.nih.gov/pubmed/24619166

“Our results indicated that food emulsifier applied in relatively high concentrations in even the most frequently consumed foods can increase the absorption of DEHP, and its role may be related to the structure and function damages of mitochondria in enterocytes.”

Toxicology Sciences • June 2014

Food emulsifier polysorbate 80 increases intestinal absorption of di-(2-ethylhexyl) phthalate in rats

Author information

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Abstract

The aim of the present research was to explore whether food emulsifier polysorbate 80 can enhance the absorption of di-(2-ethylhexyl) phthalate (DEHP) and its possible mechanism. We established the high-performance liquid chromatography (HPLC) method for detecting DEHP and its major metabolite, mono-ethylhexyl phthalate (MEHP) in rat plasma, and then examined the toxicokinetic and bioavailability of DEHP with or without polysorbate 80 in rats. The study of its mechanism to increase the absorption of phthalates demonstrated that polysorbate 80 can induce mitochondrial dysfunction in time- and concentration-dependence manners in Caco-2 cells by reducing mitochondrial membrane potential, diminishing the production of the adenosine triphosphate, and decreasing the activity of electron transport chain. Our results indicated that food emulsifier applied in relatively high concentrations in even the most frequently consumed foods can increase the absorption of DEHP, and its role may be related to the structure and function damages of mitochondria in enterocytes.

http://www.ncbi.nlm.nih.gov/pubmed/24675089

“Neonates in Neonatal Intensive Care Units in Brazil are exposed to a wide variety of **Harmful Excipients [Polysorbates and emulifiers et al.]** and **Potentially Harmful Excipients** with unpredictable results. Safer alternatives are needed, as well as further studies on the subject.”

European Journal Of Pediatrics • July 2014

Toxic excipients in medications for neonates in Brazil

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Abstract

The aim was to describe the exposure to excipients among neonates hospitalised in the neonatal intensive care unit (NICU) of a public hospital in Brasilia, Brazil. This was a retrospective study based on medicines that were prescribed electronically to neonates (≤28 days) who were admitted to the NICU of a hospital in Brasilia between January 1 and March 31, 2012. Excipients were identified from the medicine package leaflets and were classified according to toxicity. Seventy-nine infants received a total of 1,303 prescriptions comprising 77 formulations and 70 active drugs. Eighty-six excipients were identified, of which, 9 were harmful excipients (HE) and 48 were potentially harmful excipients (PHE). Almost all the neonates (98.7 %) were exposed to at least one HE and PHE. Preterm neonates (n=64; 1,502 neonate days) presented high risk of exposure to polysorbate 80 (3.26/100 neonate days), sodium hydroxide (3.39), PG (3.19) and propylparaben (3.06). Full-term neonates (n=15; 289 neonate days) presented risks in relation to phenol (4.84), ethanol (3.8) and sodium citrate (3.46).

CONCLUSION

Neonates in NICUs in Brazil are exposed to a wide variety of HE and PHE with unpredictable results. Safer alternatives are needed, as well as further studies on the subject.

http://www.ncbi.nlm.nih.gov/pubmed/24500397

Food Function • July 2014

Excipient foods:
designing food matrices that improve the oral bioavailability of pharmaceuticals and nutraceuticals

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Abstract

“The oral bioavailability of many lipophilic bioactive agents (pharmaceuticals and nutraceuticals) is limited due to various physicochemical and physiological processes: poor release from food or drug matrices; low solubility in gastrointestinal fluids; metabolism or chemical transformation within the gastrointestinal tract; low epithelium cell permeability. The bioavailability of these agents can be improved by specifically designing food matrices that control their release, solubilization, transport, metabolism, and absorption within the gastrointestinal tract. This article discusses the impact of food composition and structure on oral bioavailability, and how this knowledge can be used to design excipient foods for improving the oral bioavailability of lipophilic bioactives. Excipient foods contain ingredients or structures that may have no bioactivity themselves, but that are able to promote the bioactivity of co-ingested bioactives. These bioactives may be lipophilic drugs in pharmaceutical preparations (such as capsules, pills, or syrups) or nutraceuticals present within food matrices (such as natural or processed foods and beverages).”

http://www.ncbi.nlm.nih.gov/pubmed/24760211

Journal Of Crohns & Colitis • May 2013

Hypothesis:
Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease

Author information

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Abstract

"Crohn's disease (CD) incidence has increased over the past fifty years but the explanation is unclear. CD can be brought into remission by liquid enteral feeding, but the mechanism for this response is unknown. **We suggest that consumption of emulsifiers in processed foods may promote CD by increasing bacterial translocation**. This is supported by evidence that (i) geographical variation in CD correlates with emulsifier consumption as does the increasing incidence of CD in Japan; (ii) although CD incidence also correlates with fat consumption, the response to enteral feeding is not affected by the fat content of the feed and (iii) very small concentrations of the emulsifier polysorbate 80 enhance bacterial translocation across intestinal epithelia. Undigested emulsifiers may increase bacterial translocation, particularly in the small intestine where the mucus layer is discontinuous. The hypothesis should be testable by trials of enteral feeding with/without emulsifiers."

http://www.ncbi.nlm.nih.gov/pubmed/23360575

Food Additives And Contamination • Part A • Chemistry, Analysis, Control, Exposure And Risk Assessment • December 2013

Estimation of the dietary intake of 13 priority additives in France, Italy, the UK and Ireland as part of the FACET project

Author information

Vin K1, Connolly A, McCaffrey T, McKevitt A, O'Mahony C, Prieto M, Tennant D, Hearty A, Volatier JL.

Risk Assessment Directorate - French Agency for Food
Environmental and Occupational Health Safety (ANSES), Maisons Alfort, France

Abstract

The aim of this study was to assess the dietary exposure of 13 priority additives in four European countries (France, Italy, the UK and Ireland) using the Flavourings, Additives and Contact Materials Exposure Task (FACET) software. The studied additives were benzoates (E210-213), nitrites (E249-250) and sulphites (E220-228), butylated hydroxytoluene (E321), polysorbates (E432-436), sucroses esters and sucroglycerides (E473-474), polyglycerol esters of fatty acids (E475), stearoyl-lactylates (E481-482), sorbitan esters (E493-494 and E491-495), phosphates (E338-343/E450-452), aspartame (E951) and acesulfame (E950). A conservative approach (based on individual consumption data combined with maximum permitted levels (Tier 2)) was compared with more refined estimates (using a fitted distribution of concentrations based on data provided by the food industry (Tier 3)). These calculations demonstrated that the estimated intake is below the acceptable daily intake (ADI) for nine of the studied additives. However, there was a potential theoretical exceedance of the ADI observed for four additives at Tier 3 for high consumers (97.5th percentile) among children: E220-228 in the UK and Ireland, E432-436 and E481-482 in Ireland, Italy and the UK, and E493-494 in all countries. The mean intake of E493-494 could potentially exceed the ADI for one age group of children (aged 1-4 years) in the UK. For adults, high consumers only in all countries had a potential intake higher than the ADI for E493-494 at Tier 3 (an additive mainly found in bakery wares). All other additives examined had an intake below the ADI. Further refined exposure assessments may be warranted to provide a more in-depth investigation for those additives that exceeded the ADIs in this paper. This refinement may be undertaken by the introduction of additive occurrence data, which take into account the actual presence of these additives in the different food groups.

http://www.ncbi.nlm.nih.gov/pubmed/24304380

“Tween 80 can cause obvious vascular hyper permeability
and the effect is dose dependent, which indicated that Tween 80 can cause pseudoanaphylactoid reactions.
On the other hand, injectable Tween 80 is more security than medicinal tween 80,
the dosage of Tween 80 should be still controlled strictly so that to
decrease the incidence of pseudoanaphylactoid reactions.”

Zhongguo Zhong Yao Za Zhi • July 2012

Comparative study on pseudoanaphylactoid reactions induced by medicinal tween 80 and injectable tween 80

Author information

Wang Y1, Li C, Yi Y, Qin L, Zhao Y, Li G, Cong X, Cao S, Liang A.

Abstract

OBJECTIVE

To investigate the safety of different level of tween 80 by comparing the degree of pseudoanaphylactoid reactions (PR) induced by medicinal tween 80 and injectable tween 80.

METHOD

The analysis of vascular permeability of the mice ears: ICR mouse were divided into different test groups, the mice were intravenously injected with solutions of medicinal tween 80 and injectable tween 80 with 0.2%, 1% and 5% concentration, positive control Compound 48/80 and 5% glucose injection. All test substances were mixed with 0.4% Evans blue. The reaction and vascular permeability of the ears were observed and measured 30 min after injection. The analysis of vascular permeability of the rat’s skin: the rats were intravenous injected with 0. 6% Evans blue normal saline solution first, 10 minutes later, the same substances were intradermal administrated into the back of rats. The rats were sacrificed and the diameter of locus ceruleus and the content of Evans blue leak out were measured 20 min after injection.

RESULT

Medicinal tween 80 and injectable tween 80 with 5% concentration caused obvious vascular hyper permeability in ICR mice, but the degree of vascular hyperpermeability caused by injectable tween 80 was lighter than by medicinal tween 80. Other tween 80 didn’t cause obvious vascular hyper permeability in the ears of mouse. The solution of different concentration of tween 80 caused obvious locus ceruleus reaction in rat’s back. As for the content Evans blue leak out, there was no statistical significance between each group except positive control Compound 48/80 group.

CONCLUSION

Tween 80 can cause obvious vascular hyper permeability and the effect is dose dependent, which indicated that tween 80 can cause PR. On the other hand, injectable tween 80 is more security than medicinal tween 80, the dosage of tween 80 should be still controlled strictly so that to decrease the incidence of PR.

http://www.ncbi.nlm.nih.gov/pubmed/23019864

BMC Pediatrics • August 2012

Hospitalised neonates in Estonia commonly receive potentially harmful excipients

Author information

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Abstract

BACKGROUND

Information on the neonatal exposure to excipients is limited. Our aim was to describe the extent of excipient intake by Estonian neonates; to classify the excipients according to potential neonatal toxicity and thereby to measure the extent of exposure of neonates to potentially harmful excipients.

METHODS

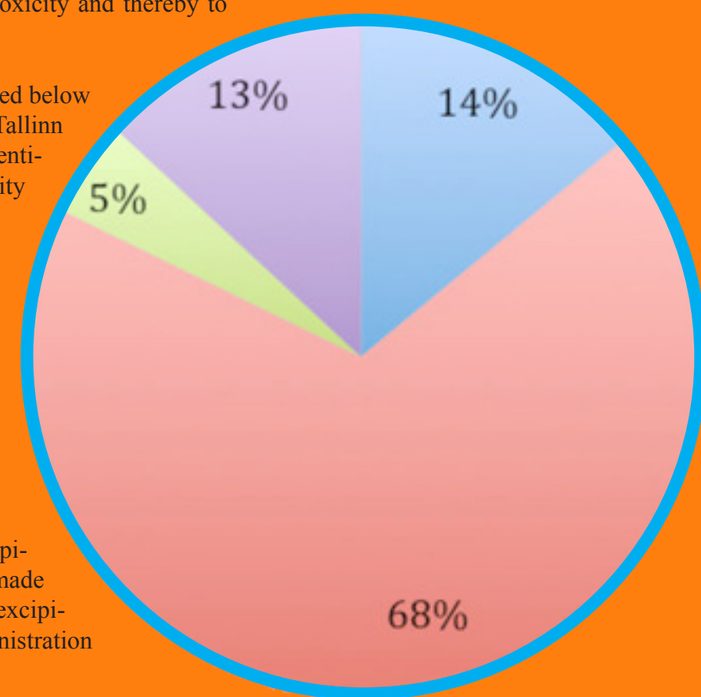
A prospective cohort study that recorded all medicines prescribed to patients aged below 28 days admitted to Tartu University Hospital from 01.02-01.08 2008 and to Tallinn Children's Hospital from 01.02- 01.08 2009 was conducted. Excipients were identified from Summaries of Product Characteristics and classified according to toxicity following a literature review.

RESULTS

1961 prescriptions comprising 107 medicines were written for 348/490 neonates admitted. A total of 123 excipients were found in 1620 (83%) prescriptions and 93 (87%) medicines. 47 (38%) of these excipients were classified as potentially or known to be harmful to neonates. Most neonates (97%) received at least one medicine (median number 2) with potentially or known to be harmful excipient. Parabens were the most commonly used known to be harmful excipients and sodium metabisulphite the most commonly used potentially harmful excipient, received by 343 (99%) and 297 (85%) of treated neonates, respectively.

CONCLUSIONS

Hospitalised neonates in Estonia are commonly receiving a wide range of excipients with their medication. Quantitative information about excipients should be made available to pharmacists and neonatologists helping them to take into account excipient issues when selecting medicines and to monitor for adverse effects if administration of medicines containing excipients is unavoidable.



Full text, graphs, charts and 31 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3483231/

“The prevalence of neonates exposed to Unlicensed, Off Label drugs during hospitalization was high ...”

Journal de Pediatrica • November 2012

Use of off-label and unlicensed drugs in the neonatal intensive care unit and its association with severity scores

Author information

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Abstract

OBJECTIVE

To analyze the frequency of unlicensed (UL) and off-label (OL) prescriptions in neonates admitted to the neonatal intensive care unit of a tertiary care hospital and to determine their association with patients' severity.

METHODS

Observational cohort study including drugs prescribed during hospitalization of neonates over a 6-week period between July and August 2011. The drugs were classified as UL and OL for dose, frequency, presentation, age group, or indication, according to an electronic list of drugs approved by the Food and Drug Administration. Patients were followed until hospital discharge or 31 days of hospitalization, with daily records of the Neonatal Therapeutic Intervention Scoring System (NTISS).

RESULTS

We identified 318 prescription items for 61 patients (average of five items/patient); there were only 13 patients with appropriate use of medications (21%). A prevalence of 7.5% was identified for UL prescriptions and 27.7% for OL, and the most prevalent OL use was that related to age group - 19.5%. Fifty-seven medications were computed - one patient received 10 UL/OL drugs during hospitalization. The prevalence of OL uses was higher in preterm infants < 35 weeks and in those with higher severity scores ($p = 0.00$).

CONCLUSIONS

The prevalence of neonates exposed to UL/OL drugs during hospitalization was high, especially for those with higher NTISS scores. Although there is general appreciation that neonates, especially preterm infants, have a high rate of drug use, an assessment including different cultures and countries is still needed to prioritize areas for future research in the pharmacotherapy of this vulnerable population.

http://www.ncbi.nlm.nih.gov/pubmed/23108602

> “In our case, we have completed the treatment without any complication after passing to another pharmaceutical form of etoposide which does not contain polysorbate-80.”

Indian Journal Of Cancer • Letter To Editor • February 2011

Etoposide? Or polysorbate-80?

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Etoposide is an antineoplastic agent from epiphodophylotoxin family. It is used in the treatment of many malignancies as intravenous and oral forms. A rare toxicity of etoposide is a hypersensitivity reaction (HSR) manifested by dyspnea, chest discomfort, hypotension, wheezing, and flushing of face. Hypersensitivity may be due to etoposide itself or the additives used in pharmaceutical form. We report here patient who, despite experiencing a HSR to intravenous etoposide, tolerated the subsequent administration of another pharmaceutical form of etoposide without any allergic reaction.

A 44-year-old male admitted to our clinic with the complaint of a mass on his neck. On physical examination, 6 cm × 8 cm mass was detected in the right anterior cervical region. On thorax tomography 10 cm × 9 cm mass filling right lung’s middle lobe and pleural effusion was detected. Tru-cut biopsy from the mass on neck was reported as non-small cell lung carcinoma with neuroendocrine pattern. He was staged as stage IIIB lung carcinoma and cisplatin with etoposide chemotherapy was started. The patient had no known allergies. Following premedication with i.v. granisetron and dexamethasone first chemo cycle was given without any complication. When the patient was admitted for the second cycle, the mass on his neck regressed to 3 cm × 2 cm and chemotherapy was continued. During the first few minutes of etoposide infusion, the patient experienced, generalized discomfort, dyspnea, flushing, chest pain, and tachycardia. On physical examination, he was found to be restless, hypotensive, and tachycardic. Electrocardiography revealed only sinus tachycardia. The infusion was immediately stopped and i.v. hydration was started. Intravenous steroid and antihistaminic was given. His complaints was completely resolved in 1 h.

The reaction might be due to etoposide itself or due to the additives used in the pharmaceutical preparation. In the literature, allergic reactions to polysorbate-80 were reported which was the solvent in the form used in this patient. Because of the distinct regression on the size of the mass, it was preferred to continue the treatment by the same combination regimen. Another etoposide preparation which did not contain polysorbate-80 was chosen to continue the treatment. With the same premedication, the treatment was administered without any reaction. It is concluded that the reaction which had occurred is more likely due to polysorbate-80 rather than etoposide itself.

The mechanism underlying HSR to etoposide has not been fully elucidated. The concentration of the drug and the rate of infusion are both accused, but there are a wide range of etoposide concentrations and rate to cause HSR to etoposide. Another possible route is that the additive used in preparation to dissolve etoposide (benzyl alcohol, polysorbate-80) may cause hypersensitivity reactions. Polysorbate-80 is a solvent used in nutritive, creams, ointments, lotions, and pharmaceutical preparations and as an additive in tablets. Although the exact mechanism of the hypersensitivity reaction is not known, it is believed to be of nonimmunugenic origin. In animal models, polysorbate-80 has been shown to cause hypersensitivity reaction by means of histamine release. It was reported that substitution of etoposide phosphate in patients with etoposide HSR seems to be appropriate In our case, we have completed the treatment without any complication after passing to another pharmaceutical form of etoposide which does not contain polysorbate-80. In some clinical situations, etoposide is an indispensable option for treatment. Especially, in such cases with HSR to etoposide, polysorbate-80 allergy should be kept in mind.

Full text with 6 references

http://www.indianjcancer.com/article.asp?issn=0019-509X;year=2011;volume=48;issue=2;spage=272;epage=273;aulast=Aksahin

“... one might expect that Polysorbate 20 with larger amounts of oleic acid will be more prone to autoxidation, thus potentially having greater impact on the oxidative degradation of the biotherapeutics it formulates.”

Analytical Chemistry • May 2011

Toward understanding molecular heterogeneity of polysorbates by application of liquid chromatography-mass spectrometry with computer-aided data analysis

Author information

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A Member of the Roche Group

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Abstract

Polysorbates (PS) are widely used as oil-in-water emulsifiers, stabilizers, wetting agents, solubilizers, and dispersants in the agricultural, food, personal care, and pharmaceutical industries due to their cost effectiveness, biocompatibility, formulation flexibility, low toxicity, and good stabilizing and protecting properties. The polysorbates are often pictured as polyoxyethylated sorbitan monoesters of saturated and/or unsaturated fatty acids. In reality, polysorbates are complex mixtures of multiple components, as follows from the reactions involved in their production. In this work, we report a novel application of liquid chromatography-mass spectrometry (LC-MS) for the characterization of polysorbates. This method takes advantage of accurate mass measurements and information on the identity of a fatty acid from “in-source” generated characteristic dioxolanylium ions. The method allowed us to perform quick profiling of fatty acids in PS 20 and 80 which, combined with a computer-aided peak assignment algorithm, facilitated detailed characterization of their constituents. As a major finding, we determined that different samples of PS 20 varied from 0% to 15% in relative amounts of unsaturated oleic acid. Although the consequences of this difference were not fully evaluated in this work, one might expect that PS 20 with larger amounts of oleic acid will be more prone to autoxidation, thus potentially having greater impact on the oxidative degradation of the biotherapeutics it formulates.

http://www.ncbi.nlm.nih.gov/pubmed/21491950

“The availability of alternative products of the same therapeutic class, but lacking specific excipient(s) should be considered in selected patients.”

Regulatory Toxicology And Pharmacology • June 2011

Excipients in medicinal products used in gastroenterology as a possible cause of side effects

Author information

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Abstract

Although most adverse drug reactions are caused by the active substances, excipients may sometimes affect the safety profile of a medicinal product. The aim of this review is twofold: (1) To identify the excipients most frequently contained in oral medicinal products marketed in Italy for gastrointestinal indications, and to evaluate the main safety concerns, considering both intrinsic toxicity and patient-related risk factors. (2) To analyze possible differences with medicinal products marketed in the United Kingdom and USA in terms of excipients and relevant warnings reported in the label. We identified excipients with potential impact on safety profile and calculated frequency of use of each identified excipient in 98 selected medicinal products. We discussed possible safety concerns in clinical practice. We also analyzed US and UK Summary of Products Characteristics (SmPC) of oral gastrointestinal products by searching in appropriate collections of regulatory agencies. Eleven excipients with a safety impact were identified (sucrose, saccharin, aspartame, sorbitol, mannitol, lactose, ethanol, propylene glycol, parabens, menthol and silica) and no substantial differences were found between drugs marketed in the three countries concerning excipient content. Warnings were more detailed in the SmPC of UK or USA products rather than Italian products. Information about pharmaceutical excipients with known effects is important in clinical practice, but the frequent lack of details in the related section of the SmPCs makes it difficult for health professionals to provide relevant advice. The availability of alternative products of the same therapeutic class, but lacking specific excipient(s) should be considered in selected patients.

http://www.ncbi.nlm.nih.gov/pubmed/21354240

“For allergies and other special populations,
there is still a certain risk to applicate polysorbate 80 in the concentration of 0.5%.
Production process of polysorbate 80 have a certain influence on allergenicity ...”

Zhongguo Zhong Yao Za Zhi • July 2011

Anaphylactoid reactions induced by polysorbate 80 on Beagle dogs

Author information

Sun W1, Li Y, Wang N, Du F, Hao W, Zhao L.
Department of Gynecology, Guang’ anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China

Abstract

OBJECTIVE
To evaluate the sensitization effect of polysorbate 80 from different factories on Beagle dogs.
METHOD
Beagles dogs were randomly divided into 5 groups, 3 in each group, received respectively the intravenous infusion of polysorbate 80 made by four factories in the concentration of 0.5%, with the constant infusing speed of 5 mL x min(-1) and volume of 10 mL x kg(-1). Changes were observed before infusion and in the 24 h after infusion, time of symptom appearance and disappearance was recorded, and the grade of response was determined. Moreover, blood pressure and heart rates were tested by the machine of Bp-98E, blood samples of animals were collected before infusion and at 10 min after ending infusion for measuring histamine content in plasma using ELISA. Then the sensitization effect was comprehensively estimated by combined consideration of the responding grade and histamine level.
RESULT
Typical symptoms of anaphylactoid reactions were found in sample 3 group, atypical symptoms were found in other polysorbate 80 groups. Different degrees of heart rate speeding and blood pressure downing were found in polysorbate 80 groups. No over 1-fold increase of plasma histamine level was found in all groups. The atypical anaphylactoid reactions and blood pressure of sample 2 group was lighter than other polysorbate 80 groups. Estimation showed that the sample 3 induced the suspicious anaphylactoid reactions, other test solutions did not induce the typical anaphylactoid reactions on Beagle dogs.
CONCLUSION
For allergies and other special populations, there is still a certain risk to applicate polysorbate 80 in the concentration of 0.5%. Production process of polysorbate 80 have a certain influence on allergenicity, refined polysorbate 80 increase the security, but further reasearchs are needed to confirmed.

http://www.ncbi.nlm.nih.gov/pubmed/22016951

AAPS PharmSciTech • December 2011

Reactive impurities in excipients: profiling, identification and mitigation of drug-excipient incompatibility

Author information

Wu Y1, Levons J, Narang AS, Raghavan K, Rao VM.

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Abstract

“**Reactive impurities in pharmaceutical excipients could cause drug product instability, leading to decreased product performance, loss in potency, and/or formation of potentially toxic degradants.** The levels of reactive impurities in excipients may vary between lots and vendors. Screening of excipients for these impurities and a thorough understanding of their potential interaction with drug candidates during early formulation development ensure robust drug product development. In this review paper, excipient impurities are categorized into six major classes, including reducing sugars, aldehydes, peroxides, metals, nitrate/nitrite, and organic acids. The sources of generation, the analytical method for detection, the stability of impurities upon storage and processing, and the potential reactions with drug candidates of these impurities are reviewed. Specific examples of drug-excipient impurity interaction from internal research and literature are provided. Mitigation strategies and corrective measures are also discussed.”

Full text, graphs, charts and 95 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3225520/

Gut • 2010

Translocation of Crohn's disease Escherichia coli across M-cells: contrasting effects of soluble plant fibres and emulsifiers

Author Information

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Abstract

Background

Crohn's disease is common in developed nations where the typical diet is low in fibre and high in processed food. Primary lesions overlie Peyer's patches and colonic lymphoid follicles where bacterial invasion through M-cells occurs. We have assessed the effect of soluble non-starch polysaccharide (NSP) and food emulsifiers on translocation of Escherichia coli across M-cells.

Methods

To assess effects of soluble plant fibres and food emulsifiers on translocation of mucosa-associated E coli isolates from Crohn's disease patients and from non-Crohn's controls, we used M-cell monolayers, generated by co-culture of Caco2-cl1 and Raji B cells, and human Peyer's patches mounted in Ussing chambers.

Results

E coli translocation increased across M-cells compared to parent Caco2-cl1 monocultures; 15.8-fold (IQR 6.2–32.0) for Crohn's disease E coli (N=8) and 6.7-fold (IQR 3.7–21.0) for control isolates (N=5). Electron microscopy confirmed E coli within M-cells. Plantain and broccoli NSP markedly reduced E coli translocation across M-cells at 5 mg/ml (range 45.3–82.6% inhibition, $p<0.01$); apple and leek NSP had no significant effect. Polysorbate-80, 0.01% vol/vol, increased E coli translocation through Caco2-cl1 monolayers 59-fold ($p<0.05$) and, at higher concentrations, increased translocation across M-cells. Similarly, E coli translocation across human Peyer's patches was reduced 45±7% by soluble plantain NSP (5 mg/ml) and increased 2-fold by polysorbate-80 (0.1% vol/vol).

Conclusions

Translocation of E coli across M-cells is reduced by soluble plant fibres, particularly plantain and broccoli, but increased by the emulsifier Polysorbate-80. These effects occur at relevant concentrations and may contribute to the impact of dietary factors on Crohn's disease pathogenesis.

Full text with Charts, Graphs and 39 references

http://gut.bmj.com/content/59/10/1331.full

"Translocation of E coli across M-cells is reduced by soluble plant fibres, particularly plantain and broccoli, but increased by the emulsifier Polysorbate-80.

These effects occur at relevant concentrations and may contribute to the impact of dietary factors on Crohn's disease pathogenesis."

“Lowered body weight was observed in male and female offspring ...”

Reproductive Toxicology • January 2008

Evaluation of developmental neurotoxicity of polysorbate 80 in rats

Author information

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Abstract

The developmental neurotoxicity of polysorbate 80 (PS80) was evaluated in rats. Crl:CD(SD) rats were given drinking water containing PS80 at 0, 0.018, 0.13, 1.0, or 7.5% (0, 0.035, 0.245, 1.864, or 16.783ml/kgbw/day) on day 0 of pregnancy through day 21 after delivery. Pregnant rats were allowed to deliver spontaneously. Potential adverse effects of pre- and post-natal exposure on the development and function of the nervous system in offspring of rats given PS80 were examined. Maternal body weight was lowered at 7.5%. Number of pups born was lowered at 7.5%. There were no compound-related effects on locomotor activity of offspring on postnatal days (PNDs) 14-15, 17-18, 20-21 and 33-37. No compound-related changes were found in developmental landmarks, sexual maturation, or reflex responses. Although decreased rate of avoidance responses was noted on PNDs 23-27 in male and female offspring at 7.5%, no compound-related changes were found in performance in the conditioned avoidance response on PNDs 60-67. Histopathological examinations of the brain revealed no toxicological changes. Lowered body weight was observed in male and female offspring at 7.5%. The NOAEL in this study was considered to be 1.0% (1.864ml/mg/kgbw/day).

http://www.ncbi.nlm.nih.gov/pubmed/17961976

“Addition of 0.1% Tween 80 not only increased the rate of oxidation in general but also altered the temperature-dependency of IL-2 mutein oxidation.”

International Journal Of Pharmacology • January 2008

Dual effects of Tween 80 on protein stability

Author information

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Abstract

In this paper, we used IL-2 mutein as a model protein and evaluated the effect of Tween 80, a non-ionic surfactant. In summary, we found that the dual effects of Tween 80 on the stability of IL-2SA, such as that shaking-induced aggregation of IL-2 mutein was significantly inhibited in the presence of Tween 80. However, this surfactant adversely affected the stability of IL-2 mutein in solution during storage in terms of both oxidation and aggregation. These adverse effects are strongly temperature and formulation-dependent. Data particularly showed that IL-2 mutein in solution forms soluble aggregates to a different degree in different formulations during storage at 40 degrees C for 2 months. Aggregation was barely detectable during storage at 5 degrees C for 22 months. Addition of 0.1% Tween 80 significantly increased the rate of IL-2 mutein aggregation during storage. The IL-2 mutein aggregates are linked by both disulfide and non-disulfide bonds and their relative contribution is temperature-dependent. IL-2 mutein can be oxidized also to a different degree in different formulations during storage and the oxidation rate is strongly temperature-dependent with an activation energy between 21 and 25 kcal/mol. Addition of 0.1% Tween 80 not only increased the rate of oxidation in general but also altered the temperature-dependency of IL-2 mutein oxidation.

http://www.ncbi.nlm.nih.gov/pubmed/17692480

“This review focuses on the chemical structure of the polysorbates, factors influencing micelle formation and factors and excipients influencing stability and degradation of the polyoxyethylene and fatty acid ester linkages.”

Journal Of Pharmaceutical Science • August 2008

Polysorbates 20 and 80 used in the formulation of protein biotherapeutics: structure and degradation pathways

Author information

AMGEN

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Abstract

Polysorbates 20 and 80 (Tween 20 and Tween 80) are used in the formulation of biotherapeutic products for both preventing surface adsorption and as stabilizers against protein aggregation. The polysorbates are amphipathic, nonionic surfactants composed of fatty acid esters of polyoxyethylene sorbitan being polyoxyethylene sorbitan monolaurate for polysorbate 20 and polyoxyethylene sorbitan monooleate for polysorbate 80. The polysorbates used in the formulation of biopharmaceuticals are mixtures of different fatty acid esters with the monolaurate fraction of polysorbate 20 making up only 40-60% of the mixture and the monooleate fraction of polysorbate 80 making up >58% of the mixture. The polysorbates undergo autooxidation, cleavage at the ethylene oxide subunits and hydrolysis of the fatty acid ester bond. Autooxidation results in hydroperoxide formation, side-chain cleavage and eventually formation of short chain acids such as formic acid all of which could influence the stability of a biopharmaceutical product. Oxidation of the fatty acid moiety while well described in the literature has not been specifically investigated for polysorbate. This review focuses on the chemical structure of the polysorbates, factors influencing micelle formation and factors and excipients influencing stability and degradation of the polyoxyethylene and fatty acid ester linkages.

http://www.ncbi.nlm.nih.gov/pubmed/17973307

“This review describes the reported effects of commonly used co-solvents and excipients on drug pharmacokinetics and on physiological systems which are likely to influence drug disposition. Such information will be useful in study design and evaluating data from pharmacokinetic experiments, so that the potential influence of formulation components can be minimized.”

Advanced Drug Delivery Reviews • December 2007

The effects of pharmaceutical excipients on drug disposition

Author information

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Abstract

Many new chemical entities are poorly soluble, requiring the use of co-solvents or excipients to produce suitable intravenous formulations for early pre-clinical development studies. There is some evidence in the literature that these formulation components can have significant physiological and physicochemical effects which may alter the distribution and elimination of co-administered drugs. Such effects have the potential to influence the results of pre-clinical pharmacokinetic studies, giving a false impression of a compound’s intrinsic pharmacokinetics and frustrating attempts to predict the drug’s ultimate clinical pharmacokinetics. This review describes the reported effects of commonly used co-solvents and excipients on drug pharmacokinetics and on physiological systems which are likely to influence drug disposition. Such information will be useful in study design and evaluating data from pharmacokinetic experiments, so that the potential influence of formulation components can be minimized.

http://www.ncbi.nlm.nih.gov/pubmed/18198495

“Therefore, we conclude that Polysorbate 80 has an immunomodulatory effect on the antigen-specific response resulting in a shift towards Th2 predominance with respect to the antigen recognition stage. Taken together, our findings suggest that PS80 might decrease the efficacy of Cry-consensus peptide through modulation of the efficiency of antigen endocytosis and/or of the direction of successive T helper cell differentiation.”

Immunology • July 2006

PS80 interferes with the antiallergic effect of Cry-consensus peptide, a novel recombinant peptide for immunotherapy of Japanese cedar pollinosis, at very low concentration through modulation of Th1/Th2 balance

Author information

Kozutsumi D1, Tsunematsu M, Yamaji T, Murakami R, Yokoyama M, Kino K.

Abstract

Polysorbate 80 (PS80 or Tween-80) is often used as an additive to promote the rapid solubilization of pharmaceuticals in aqueous solutions. We investigated whether coinjection of a minimal amount of PS80 had a modulatory effect on the immunotherapeutic effects of Cry (Cryptomeria)-consensus peptide, a novel peptide developed for the therapeutic management of Japanese cedar pollinosis, using a Cry j 1-sensitized mouse model with experimental allergic rhinitis. Subcutaneous challenge with Cry-consensus peptide plus 50 microg/ml of PS80 did not affect the antigen-specific proliferation of splenocytes, but decreased the potency of Cry-consensus peptide to inhibit antigen-specific interleukin (IL)-5 production by the cells significantly in comparison with challenge with Cry-consensus peptide alone. However, there was no significant difference between the effect of Cry-consensus peptide administration on interferon (IFN)-gamma production in the presence and absence of PS80, indicating that PS80 interfered with the T helper 1 (Th1)-dominant T helper balance induced by Cry-consensus peptide challenge. Moreover, the increase in the level of antigen-specific immunoglobulin G2a (IgG2a) induced by Cry-consensus peptide challenge was inhibited slightly but unambiguously by PS80 coinjection. These in vitro experiments indicated that PS80 induces Th2-type differentiation of T helper cells through preferential inhibition of IFN-gamma expression relative to IL-5 expression in splenocytes in a concentration-dependent manner. In naïve mice, sensitization by Cry-consensus peptide with PS80 induced antigen-specific IL-5 production more potently than sensitization by Cry-consensus peptide alone, and when PS80 was added to bone marrow-derived dendritic cells, the endocytosis of fluorescence-labelled Cry-consensus peptide was dramatically inhibited in a concentration-dependent manner. Therefore, we conclude that PS80 has an immunomodulatory effect on the antigen-specific response resulting in a shift towards Th2 predominance with respect to the antigen recognition stage. Taken together, our findings suggest that PS80 might decrease the efficacy of Cry-consensus peptide through modulation of the efficiency of antigen endocytosis and/or of the direction of successive T helper cell differentiation.

Full text, graphs, charts and 28 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1782296/

“**Polysorbate 80 at clinically-relevant concentrations** [relevant as in amounts found in foods and fluids] increases the cytotoxicity of hydrogen peroxide under the in vitro condition. Result suggests that polysorbate 80 may increase the susceptibility of cells to oxidative stress.”

Toxicology • February 2005

Polysorbate 80 increases the susceptibility to oxidative stress in rat thymocytes

Author information

Tatsuishi T1, Oyama Y, Iwase K, Yamaguchi JY,
Kobayashi M, Nishimura Y, Kanada A, Hirama S.

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Abstract

Effect of simultaneous application of polysorbate 80, a nonionic surfactant widely used in pharmaceutical products, and hydrogen peroxide on rat thymocytes was examined to see if polysorbate 80 increases the susceptibility to oxidative stress because this surfactant decreases the cellular content of glutathione. Polysorbate 80 at clinically-relevant concentrations increases the cytotoxicity of hydrogen peroxide under the in vitro condition. Result suggests that polysorbate 80 may increase the susceptibility of cells to oxidative stress.

http://www.ncbi.nlm.nih.gov/pubmed/15590117

Nephrology • June 2005

Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoietin

Author information

Steele RH1, Limaye S, Cleland B, Chow J, Suranyi MG.

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Abstract

“The following case reports are of two patients who have developed hypersensitivity reactions to the red cell growth hormones, darbepoietin and erythropoietin. The subsequent skin testing and clinical course suggested that the cause of these reactions was due to the excipient polysorbate 80. This finding might have implications in the recent increase in the incidence of pure red cell aplasia.”

http://www.ncbi.nlm.nih.gov/pubmed/15958049

“Polysorbate 80 is a ubiquitously used solubilizing agent that can cause severe nonimmunologic anaphylactoid reactions.”

Annals In Allergy, Asthma And Immunology • December 2005

Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions

Author information

Coors EA1, Seybold H, Merk HF, Mahler V.
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Abstract

BACKGROUND

Polyoxyethylene-sorbitan-20-monooleate (also known as polysorbate 80 and Tween 80) is a solubilizing agent ubiquitously used in nutritives, creams, ointments, lotions, and multiple medical preparations (e.g., vitamin oils, vaccines, and anticancer agents) and as an additive in tablets. Whereas its relevance as a contact allergen has declined during the past decades, it is of current relevance as a “hidden” inductor of anaphylactoid reactions.

OBJECTIVE

To identify polysorbate 80 (generally believed to be an inert vehicle) as an inductor of a severe anaphylactoid reaction.

METHODS

Skin prick testing, enzyme-linked immunosorbent assay, IgE immunoblotting, and flow cytometric detection of basophil activation were performed in controls and in a patient with a medical history of anaphylactic shock due to intravenous administration of a multivitamin product during pregnancy.

RESULTS

Polysorbate 80 was identified as the causative agent for the anaphylactoid reaction of nonimmunologic origin in the patient. Polysorbate specific IgE antibodies were not identified in enzyme-linked immunosorbent assay and immunoblot examinations, confirming the nonimmunologic nature of the anaphylactoid reaction.

CONCLUSIONS

Polysorbate 80 is a ubiquitously used solubilizing agent that can cause severe nonimmunologic anaphylactoid reactions.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16400901

“Thus, a direct inhibition of the metabolizing enzymes,
a molecular interaction with the microsomes as well as an alteration of membrane properties
that did not yet result in a release of LDH have to be taken into consideration
as reasons for the observed changes in the metabolism of midazolam.”

Biopharmaceutics And Drug Disposition • January 2004

In vitro investigation on the impact of the surface-active excipients Cremophor EL, Tween 80 and Solutol HS 15 on the metabolism of midazolam

Author information

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Abstract

The impact of the surface-active formulation ingredients Cremophor EL, Tween 80 and Solutol HS 15 on the intrinsic clearance (Clint) of midazolam (MDZ) was investigated in rat hepatocytes and microsomes. In rat hepatocytes with 0.003%, 0.03% and 0.3% (w/v) Solutol HS 15 already present in the incubation medium, the Clint was significantly reduced in a dose-dependent manner by about 25%, 30% and 50%, respectively. In the presence of Cremophor EL and Tween 80 a significant reduction in Clint by about 30% and 25%, respectively, was observed at 0.03% surfactant concentration. At 0.3% of Cremophor EL and Tween 80, Clint was reduced by about 50% and 20%, respectively. A reduction in Clint was also observed in experiments with rat liver microsomes. At surfactant concentrations up to 0.03%, cytotoxicity assays (lactate dehydrogenase release, adenosine triphosphate content) as well as light microscope investigations did not reveal any cytotoxic impact of the surfactants on the hepatocyte monolayer. A potential interaction of the surfactants with biological membranes was determined using phosphatidylcholine-cholesterol liposomes loaded with self-quenching concentrations of carboxyfluorescein. No marked release of carboxyfluorescein from the liposomes (that would be an indication for a surfactant-dependent disruption of membrane integrity) was observed up to concentrations of 0.03% of the different surfactants. It is concluded that cytochrome P450 3A mediated metabolism of MDZ seems to be prevented by all surfactants at concentrations above 0.03%. In our experiments the surfactants did not show toxic effects at concentrations that resulted in a decreased Clint of MDZ. Thus, a direct inhibition of the metabolizing enzymes, a molecular interaction with the microsomes as well as an alteration of membrane properties that did not yet result in a release of LDH have to be taken into consideration as reasons for the observed changes in the metabolism of MDZ.

http://www.ncbi.nlm.nih.gov/pubmed/14716751

“These studies show that many excipients/surfactants can modify the pharmacokinetics of orally administered drugs that are P-gp substrates.”

International Journal Of Pharmacology • June 2004

Impact of excipients on the absorption of P-glycoprotein substrates in vitro and in vivo

Author information

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Abstract

The efflux transporter, P-glycoprotein (P-gp), located in the apical membranes of intestinal absorptive cells, can reduce the bioavailability of a wide range of orally administered drugs. A number of surfactants/excipients have been shown to inhibit P-gp, and thus potentially enhance drug absorption. In this study, the improved everted gut sac technique was used to screen excipients for their ability to enhance the absorption of digoxin and celiprolol in vitro. The most effective excipients with digoxin were (at 0.5%, w/v): Labrasol > Imwitor 742 > Acconon E = Softigen 767 > Cremophor EL > Miglyol > Solutol HS 15 > Sucrose monolaurate > Polysorbate 20 > TPGS > Polysorbate 80. With celiprolol, Cremophor EL and Acconon E had no effect, but transport was enhanced by Softigen 767 > TPGS > Imwitor 742. In vivo, the excipients changed the pharmacokinetic profile of orally administered digoxin or celiprolol, but without increasing the overall AUC. The most consistent change was an early peak of absorption, probably due to the higher concentration of excipient in the proximal intestine where the expression of P-gp is lower. These studies show that many excipients/surfactants can modify the pharmacokinetics of orally administered drugs that are P-gp substrates.

http://www.ncbi.nlm.nih.gov/pubmed/15158955

“It can be suggested that polysorbate 80 modifies some of membranes and intracellular physiological parameters without affecting the cell viability.”

Toxicology • July 2004

Flow-cytometric analysis on adverse effects of polysorbate 80 in rat thymocytes

Author information

Hirama S1, Tatsuishi T, Iwase K, Nakao H, Umebayashi C, Nishizaki Y, Kobayashi M, Ishida S, Okano Y, Oyama Y.

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Abstract

The effects of polysorbate 80, a non-ionic surfactant widely used in pharmaceutical products, on rat thymocytes were examined to reveal its toxic property at the cellular level. Polysorbate 80 at concentrations of 1-100 microg/ml did not significantly affect the cell viability. This surfactant at 30 microg/ml or more augmented the intensity of fluo-3 fluorescence, indicating the increase in intracellular Ca(2+) concentration. Such an augmentation of fluo-3 fluorescence by polysorbate 80 was not seen under the Ca(2+)-free condition, suggesting that polysorbate 80 increased membrane Ca(2+) permeability. The concentration-dependent polysorbate 80 at 10 microg/ml or more attenuated the intensity of 5-chloromethylfluorescein, indicating a decrease in cellular content of glutathione by polysorbate 80. Furthermore, the agent at 1 microg/ml or more attenuated the intensity of bis-(1,3-dibutylbarbituric acid) trimethine oxonol fluorescence, being independent from the changes in membrane potential. This phenomenon indicates that polysorbate 80 at 1 microg/ml or more may attenuate the incorporation of anionic compounds into the membranes. It can be suggested that polysorbate 80 modifies some of membranes and intracellular physiological parameters without affecting the cell viability.

http://www.ncbi.nlm.nih.gov/pubmed/15147788

“In conclusion, we demonstrate that the detergents Tween 80 and Triton X-100 are potent inhibitors of neuronal nACh alpha(7) receptors expressed in Xenopus oocytes, and we suggest that studies utilizing these detergents to solubilize lipophilic drugs should be scrutinized for such effects.”

Journal Of Neuroscience Methods • August 2004

The solubilizing detergents, Tween 80 and Triton X-100 non-competitively inhibit alpha 7-nicotinic acetylcholine receptor function in Xenopus oocytes

Author information

Oz M1, Spivak CE, Lupica CR.

Abstract

Because many studies rely upon detergents to solubilize lipophilic agents such as cannabinoid drugs, we examined the effect of commonly employed detergents on the function of the cloned alpha(7) subunit of the nicotinic ACh receptor. Homomeric alpha(7) receptors were expressed in Xenopus oocytes and the two-microelectrode voltage-clamp technique was used to assess their electrophysiological properties. The detergents Tween 80 and Triton X-100 reversibly inhibited ACh (100 microM)-induced inward currents in a concentration-dependent manner, with IC(50) values of 610 nM and 1.4 microM, respectively. The effects of these detergents were independent of membrane potential, and they were not mediated by endogenous Ca(2+)-dependent Cl(-) channels, since they were unaffected by intracellularly injected BAPTA, and recorded in Ca(2+)-free bathing solution containing 2 mM Ba(2+). Both detergents also decreased the maximal effect of ACh, without significantly affecting its EC(50), indicating a non-competitive interaction with the nACh alpha(7) receptors. In contrast to the effects of these detergents, we found that cholic acid (10 microM), DMSO (10 microM) and Tocrisol (0.01% v/v) did not cause a significant effect on nicotinic responses. In conclusion, we demonstrate that the detergents Tween 80 and Triton X-100 are potent inhibitors of neuronal nACh alpha(7) receptors expressed in Xenopus oocytes, and we suggest that studies utilizing these detergents to solubilize lipophilic drugs should be scrutinized for such effects.

http://www.ncbi.nlm.nih.gov/pubmed/15262057

“In conclusion, Tween 80 at 1 or 10% (w/w) doses can improve the efficiency of the digestive system to absorb dietary fat but at high concentrations (10%, w/w) it appeared to have a toxic or irritating effect on the gastrointestinal system. More importantly, the effect of Tween 80 on size and number of chylomicrons is a condition that favours a delay in their clearance rate.”

Food Chemistry And Toxicology • April 2003

Effect of a surfactant, Tween 80, on the formation and secretion of chylomicrons in the rat

Author information

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Abstract

Effects of Tween 80, a nonionic surfactant, on size and number of chylomicrons (CM) secreted during lipid absorption in the rat model are reported. Fasted rats were loaded with either 154 mM NaCl or 25% (w/w) olive oil emulsion in 154 mM NaCl with 0, 0.1, 1 or 10% (w/w) Tween 80. After 3 h, either mesenteric lymph or blood was collected and their triacylglycerol-rich lipoprotein fraction (Sf>20 and Sf>400, respectively) isolated. Triacylglycerol (TAG) and apolipoprotein B48 (apoB48) concentrations in the lipoprotein fractions were assayed and their fluxes (lymph) calculated. TAG:apoB48 ratios, indicative of CM size, were determined. The data support the hypothesis that fat loading is accommodated mainly by increased average size, rather than number, of CM. Co-administration of Tween 80 with olive oil resulted in a significant increase in CM apoB48 secretion into the mesenteric lymph duct and in an increased concentration of apoB48 in the blood (Sf>400). Also, Tween 80-treated groups exhibited smaller mean CM size relative to the olive oil only group in both lymph and blood. The observed effect on CM size and number did not appear to be dose dependent at concentrations of Tween 80 above 0.1% (w/w). Incorporation of Tween 80 in the diet at 1 or 10% (w/w) concentrations reduced the TAG concentration in the stools; however, a significant increase in water content was observed at 10% (w/w) concentration. In conclusion, Tween 80 at 1 or 10% (w/w) doses can improve the efficiency of the digestive system to absorb dietary fat but at high concentrations (10%, w/w) it appeared to have a toxic or irritating effect on the gastrointestinal system. More importantly, the effect of Tween 80 on size and number of CM is a condition that favours a delay in their clearance rate.

http://www.ncbi.nlm.nih.gov/pubmed/12615130

Journal Of Pharmaceutical Science • October 2002

Peroxide formation in polysorbate 80 and protein stability

Author information

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Abstract

Nonionic surfactants are widely used in the development of protein pharmaceuticals. However, the low level of residual peroxides in surfactants can potentially affect the stability of oxidation-sensitive proteins. In this report, we examined the peroxide formation in polysorbate 80 under a variety of storage conditions and tested the potential of peroxides in polysorbate 80 to oxidize a model protein, IL-2 mutein. For the first time, we demonstrated that peroxides can be easily generated in neat polysorbate 80 in the presence of air during incubation at elevated temperatures. Polysorbate 80 in aqueous solution exhibited a faster rate of peroxide formation and a greater amount of peroxides during incubation, which is further promoted/catalyzed by light. Peroxide formation can be greatly inhibited by preventing any contact with air/oxygen during storage. IL-2 mutein can be easily oxidized both in liquid and solid states. A lower level of peroxides in polysorbate 80 did not change the rate of IL-2 mutein oxidation in liquid state but significantly accelerated its oxidation in solid state under air. A higher level of peroxides in polysorbate 80 caused a significant increase in IL-2 mutein oxidation both in liquid and solid states, and glutathione can significantly inhibit the peroxide-induced oxidation of IL-2 mutein in a lyophilized formulation. In addition, a higher level of peroxides in polysorbate 80 caused immediate IL-2 mutein oxidation during annealing in lyophilization, suggesting that implementation of an annealing step needs to be carefully evaluated in the development of a lyophilization process for oxidation-sensitive proteins in the presence of polysorbate.

http://www.ncbi.nlm.nih.gov/pubmed/12226852

“A non specific permeabilization of the Blood Brain Barrier, probably related to the toxicity of the carrier, may account for the Central Nervous System penetration of dalargin associated with polybutylcyanoacrylate nanoparticles and polysorbate 80.”

Pharmaceutical Research • December 1999

Indirect evidence that drug brain targeting using polysorbate 80-coated polybutylcyanoacrylate nanoparticles is related to toxicity

Author information

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Abstract

PURPOSE

To investigate the mechanism underlying the entry of the analgesic peptide dalargin into brain using biodegradable polybutylcyanoacrylate (PBCA) nanoparticles (NP) overcoated with polysorbate 80.

METHODS

The investigations were carried out with PBCA NP and with non biodegradable polystyrene (PS) NP (200 nm diameter). Dalargin adsorption was assessed by HPLC. Its entry into the CNS in mice was evaluated using the tail-flick procedure. Locomotor activity measurements were performed to compare NP toxicities. BBB permeabilization by PBCA NP was studied in vitro using a coculture of bovine brain capillary endothelial cells and rat astrocytes.

RESULTS

Dalargin loading was 11.7 microg/mg on PBCA NP and 16.5 microg/ mg on PS NP. Adding polysorbate 80 to NP led to a complete desorption. Nevertheless, dalargin associated with PBCA NP and polysorbate 80 induced a potent and prolonged analgesia, which could not be obtained using PS NP in place of PBCA NP. Locomotor activity dramatically decreased in mice dosed with PBCA NP, but not with PS NP. PBCA NP also caused occasional mortality. In vitro, PBCA NP (10 microg/ml) induced a permeabilization of the BBB model.

CONCLUSIONS

A non specific permeabilization of the BBB, probably related to the toxicity of the carrier, may account for the CNS penetration of dalargin associated with PBCA NP and polysorbate 80.

http://www.ncbi.nlm.nih.gov/pubmed/10644071

“The results indicate that allergens are present in Tween 80 before oxidation and that new allergens are formed in the oxidation process. No obvious dose-response relationship was found in the sensitization studies. The possibility that allergenic compounds can be formed during storage and handling of products containing ethoxylated surfactants should be taken into consideration.”

Contact Dermatitis • July 1997

Contact allergenic activity of Tween 80 before and after air exposure

Author information

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Department of Occupational Health, National Institute for Working Life, Solna, Sweden

Abstract

Tween 80 is an ethoxylated hydrophilic non-ionic surfactant, which is used for the preparation of oil-in-water emulsions in pharmaceutical products, cosmetics, and industrial detergents. Ethoxylated surfactants are polyethers and are thus easily oxidized by atmospheric oxygen to a variety of hydroperoxides, peroxides and carbonyl compounds. The aim was to investigate the formation of oxidation products and the allergenic potential of Tween 80 before and after air exposure. The formation of peroxides and formaldehyde was followed with chemical analyses during air and pure oxygen exposure of water solutions of Tween 80 of technical quality. A complex mixture of compounds was formed when Tween 80 was oxidized. Formaldehyde was detected in amounts that may be eliciting in allergic individuals. Acetaldehyde was identified in Tween 80 before oxygen exposure, whereafter the amount gradually decreased. The contact allergenic activity was determined in experimental sensitization studies in guinea pigs. Non-oxidized as well as oxidized Tween 80 of technical quality showed allergenic activity. The results indicate that allergens are present in Tween 80 before oxidation and that new allergens are formed in the oxidation process. No obvious dose-response relationship was found in the sensitization studies. The possibility that allergenic compounds can be formed during storage and handling of products containing ethoxylated surfactants should be taken into consideration.

http://www.ncbi.nlm.nih.gov/pubmed/9255480

“These data suggest that the mechanism underlying the reduction in the release of endothelium derived relaxing factor from donor aorta segments may be the destruction by Tween 80 of endothelial lining.”

Research Communications In Molecular Pathology And Pharmacology • February 1996

Tween 80 and endothelium: functional reduction due to tissue damage

Author information

Uluoglu C1, Korkusuz P, Uluoglu O, Zengil H.

Abstract

The effects of Tween 80, a surface active agent which is frequently used for dispersion of water-insoluble substances, on endothelial function in rabbit aorta, were investigated in a cascade superfusion bioassay system by using a deendothelized precontracted rat aorta ring as a bioassay tissue. Prior incubation of rabbit thoracic aorta segments with higher concentrations of Tween 80, caused total inhibition of acetylcholine-induced endothelium derived relaxing factor (EDRF) release, while moderate concentrations had no significant effect. Perfusion of the donor aortae segments with 10 (-1) - 10 (-3) ml/1 Tween 80 also inhibited the EDRF release from donor aorta dose-dependently. Histopathological examination of the vasculary wall and endothelial structures revealed a significant desquamation of vasculary endothelium with the highest concentration of Tween 80 used in this study. These data suggest that the mechanism underlying the reduction in the release of EDRF from donor aorta segments may be the destruction by Tween 80 of endothelial lining.

http://www.ncbi.nlm.nih.gov/pubmed/8832909

“Both etoposide and its excipient (polysorbate 80) are suspected of causing hypersensitivity reactions.”

Annals In Pharmacotherapy • April 1996

Hypersensitivity reactions to etoposide

Author information
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Department of Pharmacy, Slotervaart Hospital, Amsterdam, Netherlands

Abstract

OBJECTIVE
To report a hypersensitivity reaction to etoposide occurring in a patient after 2 months of drug therapy.
CASE SUMMARY
A 20-year-old man with a diagnosis of testicular carcinoma was treated with bleomycin, etoposide, and cisplatin (BEP regimen). After dose 20 of etoposide, an exanthema was noted, which was attributed to etoposide. The patient had received 19 doses of etoposide during the previous 2 months without any sign of an allergic reaction. Rechallenging the patient with etoposide from another batch resulted in recurrence of the exanthema.
DISCUSSION
Both etoposide and its excipient (polysorbate 80) are suspected of causing hypersensitivity reactions. Although the exact mechanism of the hypersensitivity reaction is not known, it is believed to be of nonimmunogenic origin.
CONCLUSIONS
With a lower rate of infusion of etoposide and/or by premedication with antihistamines and/or corticosteroids, hypersensitivity reactions to etoposide might be prevented in patients with a history of hypersensitivity to this drug.

http://www.ncbi.nlm.nih.gov/pubmed/8729891

International Journal Of Tissue Reactions • June 1996

Convulsions and death induced in rats by Tween 80 are prevented by capsaicin

Author information

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Faculté de Médecine Grange-Blanche, Université Claude Bernard, Lyon, France

Abstract

"Two or three minutes after intracerebroventricular (i.c.v.) injection of Tween 80 plus ethanol as vehicles for capsaicin, strong convulsive movements occurred in the treated rats; they twisted and turned, dashed themselves against their cage and all died. Tween 80 in saline without ethanol also produced convulsions and death in all the rats treated. Capsaicin dissolved in the vehicle seemed to furnish protection against such death. Moreover, when capsaicin in Tween 80 was administered i.c.v. 10 min before the Tween vehicle it prevented the death which would have been caused by the i.c.v. vehicle. Thus a new effect is added to those already discovered in the numerous pharmacological studies on capsaicin."

http://www.ncbi.nlm.nih.gov/pubmed/8880377

“Tween 80 inhibited the contractile effects of 5-hydroxytryptamine, phenylephrine, and bradykinin significantly. The data suggests that these substances affect both endothelial cells and vascular smooth muscle.”

Experientia • November 1995

Effects of polysorbates and Cremophor EL on vascular responses in rat aorta

Author information

Zengil H1, Hodoglugil U, Güney Z.
Department of Pharmacology, Gazi University Medical School, Ankara, Turkey

Abstract

The effects of Tween 20, Tween 80, and Cremophor EL, surface active agents which are used for dispersion of water-insoluble substances, on vascular responsiveness were investigated using rat aortic rings. In high concentrations all these agents produced persistent contractions in aortic rings independent of the presence of endothelium. These contractions were not influenced by inhibitors of known endogenous contractile mediators. Incubation with these agents caused a concentration-dependent inhibition of the endothelium-dependent relaxant responses to acetylcholine in intact precontracted aortic rings. Endothelium-independent relaxations produced by sodium nitroprusside were not inhibited, but rather potentiated in the presence of Tween 80 (10(-1) ml/l). On the other hand, Tween 80 inhibited the contractile effects of 5-hydroxytryptamine, phenylephrine, and bradykinin significantly. The data suggests that these substances affect both endothelial cells and vascular smooth muscle.

http://www.ncbi.nlm.nih.gov/pubmed/7498444

“Treatment with Tween 80 accelerated maturation, prolonged the oestrus cycle, and induced persistent vaginal oestrus. The relative weight of the uterus and ovaries was decreased relative to the untreated controls. Squamous cell metaplasia of the epithelial lining of the uterus and cytological changes in the uterus were indicative of chronic oestrogenic stimulation. Ovaries were without corpora lutea, and had degenerative follicles.”

Food Chemistry And Toxicology • March 1993

Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats

Author information

Gajdová M1, Jakubovsky J, Války J.

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Abstract

Neonatal female rats were injected ip (0.1 ml/rat) with Tween 80 in 1, 5 or 10% aqueous solution on days 4-7 after birth. Treatment with Tween 80 accelerated maturation, prolonged the oestrus cycle, and induced persistent vaginal oestrus. The relative weight of the uterus and ovaries was decreased relative to the untreated controls. Squamous cell metaplasia of the epithelial lining of the uterus and cytological changes in the uterus were indicative of chronic oestrogenic stimulation. Ovaries were without corpora lutea, and had degenerative follicles.

http://www.ncbi.nlm.nih.gov/pubmed/8473002

JPEN Journal Of Parenteral And Enteral Nutrition • March 1990

Parenteral nutrition hypersensitivity

Author information

Levy M1, Dupuis LL.

Department of Paediatrics, Hospital for Sick Children, Toronto, Canada

Abstract

“Total parenteral nutrition (TPN) is widely used. Although mechanical, septic, and metabolic complications are well known, hypersensitivity skin reactions are rare. We describe a 16-year-old boy with Burkitt’s lymphoma who developed a urticarial skin rash when treated with TPN and vitamins. The adverse skin reaction was probably caused by the inactive component of excipient, polysorbate.”

http://www.ncbi.nlm.nih.gov/pubmed/2112631

Pediatrics • April 1986

Polysorbate 80 and E-Ferol toxicity

Alade SL, Brown RE, Paquet A Jr.

Abstract

“The relatively recent introduction and use of an intravenous form of a vitamin E preparation (E-Ferol) has been associated with the development of an unusual syndrome and fatalities among low birth weight (less than 1,500 g), premature infants in neonatal intensive care units. We have observed an inhibitory effect by this vitamin E preparation on the in vitro response of human lymphocytes to phytohemagglutinin (PHA). E-Ferol suppressed the expected response to low doses of PHA. However, this suppression was not due to the alpha-tocopherol acetate (vitamin E) component, because alpha-tocopherol acetate by itself was not inhibitory; in fact, it often enhanced the PHA response. Because a mixture of polysorbate 80 and polysorbate 20 is used as a carrier in E-Ferol, these components were also tested and were found to be responsible for the suppression, especially the polysorbate 80. Concurrent with this suppression of PHA-induced mitogenesis was a decrease in the percentage of T11 lymphocytes.”

http://www.ncbi.nlm.nih.gov/pubmed/3960626

“The results of the present study indicate that polysorbate 80 can neither be used as a solvent for isolated tissue experiments nor when considered for intravenous administration.”

Arzneimittelforschung • June 1985

Polysorbate 80: a pharmacological study

Varma RK, Kaushal R, Junnarkar AY, Thomas GP, Naidu MU, Singh PP, Tripathi RM, Shridhar DR.

Abstract

Polyoxyethylene (20) sorbitan monooleate (polysorbate 80, Tween 80), a surfactant, has been widely used as a solvent for pharmacological experiments. In the present study, polysorbate 80 was found to have toxicity of a low order in both the mice and rats when given by i.p. and p.o. routes. It produced mild to moderate depression of the central nervous system with a marked reduction in locomotor activity and rectal temperature, exhibited ataxia and paralytic activity and potentiated the pentobarbital sleeping time. On intravenous administration in dogs, it had a dose-dependent hypotensive effect. Polysorbate 80 did not have a direct stimulant or relaxant effect on either guinea pig ileum or rat uterus, however, it antagonised the contractions induced by acetylcholine, histamine, barium, 5-hydroxytryptamine and carbachol in a dose-dependent manner. A direct relaxant effect was observed on rabbit jejunum. A dose-dependent myocardial depressant effect was observed on guinea pig and rabbit paired atrial preparations. On the electrically-driven guinea pig left atrial preparation, polysorbate 80 exhibited a dose-dependent negative inotropic action. Polysorbate 80 did not induce diuresis in rats upto a dose of 2.5 ml/kg. The results of the present study indicate that polysorbate 80 can neither be used as a solvent for isolated tissue experiments nor when considered for intravenous administration. However, polysorbate 80 can be employed safely as a vehicle for neuropsychopharmacological experiments in doses not exceeding 1 ml/kg.

http://www.ncbi.nlm.nih.gov/pubmed/4026903

Life Science • June 1982

Effect of Tween 80 on exploratory behavior and locomotor activity in rats

Brubaker CM, Taylor DH, Bull RJ.

Abstract

“Exploratory behavior and locomotor activity is enhanced in male rat pups (aged 10 to 20 days) whose dams received a chronic dose (1.25 ml/l) of Tween 80 via their drinking water. This enhancement manifests itself during the diurnal period of the day. These data suggest that Tween 80 has an effect on the CNS which could lead to misinterpretation of results in toxicology studies that use this compound as a dosage vehicle.”

http://www.ncbi.nlm.nih.gov/pubmed/7202094

International Archives In Allergy And Applied Immunology • June 1981

Immunosuppressive effects of tween 80 on mice

By J.B. Barnett

Abstract

"The effects of Tween 80 on the humoral immune response, as measured by the Jerne plaque assay, was determined. Mice treated with Tween 80 showed a significant depression in the number of primary (IgM) plaques without a significant difference in the number of secondary (IgG) plaques. In addition, the cell-mediated responses were assessed by contact hypersensitivity to oxazolone. Mice treated with Tween 80 showed no significant decrease in contact sensitivity. Thus, the suppression caused by Tween 80 affected only the primary humoral immune response."

http://www.ncbi.nlm.nih.gov/pubmed/7026458

“These results indicate that although the retinol component of retinol:
Tween 80 caused an immunopotentiation, the Tween 80 component effected a temporary suppression.”

International Archives Of Allergy And Applied Immunology • July 1980

Adjuvant and immunosuppressive effects of retinol and Tween 80 on IgG production in mice

Barnett JB, Bryant RL.

Abstract

The effect of retinol emulsified in Tween 80, alone or in combination with Al(OH)3, on the adjuvant-independent and dependent IgG responses to ovalbumin (OA) were examined by passive hemagglutination and passive cutaneous anaphylaxis, respectively. High antibody levels were detected after a second injection of OA on day 30, however, primary IgG antibodies were either partially (adjuvant independent) or totally (adjuvant dependent) suppressed. Animals treated with saline:Tween 80 prior to immunization with OA in saline as a control produced no detectable antibody response after either antigen injection. Additional control animals pretreated with saline:Tween 80 and then immunized with OA absorbed to Al(OH)3 [OA:Al(OH)3] showed suppressed primary responses and a significant increase in antibody levels after a second injection of OA:Al(OH)3. These results indicate that although the retinol component of retinol: Tween 80 caused an immunopotentiation, the Tween 80 component effected a temporary suppression.

http://www.ncbi.nlm.nih.gov/pubmed/7419282

Infections And Immunity • May 1979

Influence of oil and Tween concentrations on enhanced endotoxin lethality in mice pretreated with emulsified trehalose-6,6'-dimycolate (cord factor)

Yarkoni E, Rapp HJ.

Abstract

"Susceptibility to the lethal toxicity of endotoxin in mice pretreated with emulsified trehalose-6,6'-dimycolate was enhanced by (i) increasing the oil concentration while keeping the Tween concentration constant; and (ii) decreasing the Tween concentration, while keeping the oil concentration constant."

Full text with 10 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC414340/

Cancer Research • November 1975

Potential carcinogenicity of food additives and contaminants

By P. Shubik

Abstract

“The potential role in carcinogenesis of food additives and contaminants presents a complex problem in terms of assessing the risk to the general public. Long-term testing in laboratory animals is still the most feasible method for determining potential carcinogenicity of various chemicals. The disadvantages encountered in the present methods of animal testing are discussed and a review is made of the current status of particular food additives and contaminants under scrutiny as possible carcinogens. It is suggested that, since it may not be possible to remove all carcinogenic materials from the environment, methods to mitigate or neutralize their harmful effects should be sought. Greater cooperation is called for among food technologists, toxicologists, laboratory researchers, and epidemiologists in the decision-making process regarding the role of possibly carcinogenic additives and contaminants.”

Full text PDF with 20 references

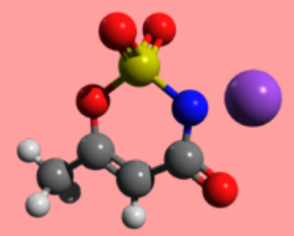
http://cancerres.aacrjournals.org/content/canres/35/11_Part_2/3475.full.pdf

CHAPTER SIX

Artificial Sweeteners & Sugar

The food and beverage industry is increasingly replacing sugar or corn syrup with artificial sweeteners in a range of products traditionally containing sugar.

According to market analysts Mintel, a total of 3,920 products containing artificial sweeteners were launched in the U.S. between 2000 and 2005. In 2004 alone, 1,649 artificially sweetened products were launched. According to market analysts Freedonia, the United States artificial sweetener market is set to grow at around 8% per year to $189 million by 2012.



Aspartame is currently the most popular artificial sweetener in the U.S. food industry, as the price has dropped significantly since the Monsanto Company patent expired in 1992. However, sucralose may soon replace it, as alternative processes to Tate & Lyle's patent seem to be emerging. According to Morgan Stanley, this can mean that the price of sucralose will drop by thirty percent.

The Peer Review

Aspartame
Sucralose
Saccharin
Acesulfame Potassium or Acesulfame K
Neotame
Cyclamate
Erythritol
Glycerol
Lactitol
Maltitol
Mannitol
Polydextrose
Sorbitol
Xylitol
HFCS
Stevia
Sugar

Alternative sweeteners are highly consumed in America. In 2003–2004, Americans two years of age and older consumed 585 grams (21 oz) per day of beverages and 375 grams (13 oz) per day of foods with caloric sweeteners. More than 66% of Americans consumed these beverages with alternative sweeteners and 82.3% of Americans consumed foods with added caloric sweeteners. On the other hand, 10.8% of Americans in 2003–2004 consumed non-caloric alternative sweetener flavored beverages and 5.8% consumed non-caloric alternative sweetener flavored foods.

WEIGHT GAIN & ARTIFICIAL SWEETENERS

Animal studies have indicated that a sweet taste induces an insulin response in rats. The release of insulin causes blood sugar to be stored in tissues (including fat). In the case of a response to artificial sweeteners, even if blood sugar does not increase, there can be increased hypoglycemia or hyperinsulinemia and increased food intake the next time there is a meal. Rats given sweeteners have steadily increased calorie intake, increased

body weight, and increased fatness. Furthermore, the natural responses to eating sugary foods—eating less at the next meal and using some of the extra calories to warm the body after the sugary meal—are gradually lost. A 2014 study by a collaboration of seventeen scientists from nine Israeli research institutes presented experimental evidence that artificial sweeteners ***may exacerbate, rather than prevent***, metabolic disorders such as Type 2 diabetes. They reported that artificial sweeteners increase the blood sugar levels in both mice and humans by altering the composition and function of the gut flora. Excessive blood sugar levels are an early indicator of Type 2 diabetes and metabolic disease. Mice given drinking water supplemented with artificial sweetener (commercial formulations of saccharin, sucralose or aspartame) developed greater glucose intolerance than mice drinking pure water, or water with only sugar added. The effect occurred both in mice fed standard food and those on a high-fat diet. Changes in the composition of the gut flora were observed by sequencing a ribosomal RNA gene. When antibiotics were then used to kill off gut bacteria, the degree of glucose intolerance in mice fed either diet was restored to normal levels present before artificial sweetener was introduced. Human subjects were also studied. Gut bacteria from 381 non-diabetics averaging age 43 were analyzed, revealing differences in the gut bacteria between those subjects who habitually consumed artificial sweeteners and those who did not, as well as "markers" for diabetes, such as raised blood sugar levels and glucose intolerance. The researchers noted that the increase in human consumption of artificial sweeteners coincides with the modern epidemic incidence of obesity and diabetes. In a journal commentary, two researchers opined that artificial sweeteners "***may contribute to, rather than alleviate, obesity-related metabolic conditions, by altering the composition and function of bacterial populations in the gut***".

Alternative sweeteners are found in many products today due to their low or non-caloric characteristics. They're extremely inexpensive and because they work on the same brain receptors as cocaine, nicotine and methamphetamine these sweeteners are highly addictive. Increase your fruit intake and avoid all of these natural and artificial sweeteners.

THE SUGARS

NATURAL SUGAR SUBSTITUTES
The sweetnesses and energy densities are in comparison to those of sucrose

Name	Sweetness by weight	Sweetness by food energy	Energy density
Brazzein	800		
Curculin	550		
Erythritol	0.7	14	0.05
Glycyrrhizin	50		
Glycerol	0.6	0.55	1.075
E422			
Inulin			
Isomalt	0.45–0.65	0.9–1.3	0.5
Lactitol	0.4	0.8	0.5
Mogroside mix	300		
Mabinlin	100		
Maltitol	0.9	1.7	0.525
Mannitol	0.5	1.2	0.4
Miraculin			

A protein that does not taste sweet by itself but modifies taste receptors to make sour things taste sweet temporarily is called Monatin and a naturally occurring sweetener isolated from the plant Sclerochiton ilicifolius called Monellin has a sweetness by weight of 3,000.

Osladin			
Pentadin	500		
Sorbitol	0.6	0.9	0.65
Stevia	250		
Tagatose	0.92	2.4	0.38
Thaumatin	2,000		
Xylitol	1.0	1.7	0.6

ARTIFICIAL SUGAR SUBSTITUTES
NON-NUTRITIVE SWEETENERS

Comparison of sweetness based on energy content is not meaningful because many artificial sweeteners have little or no food energy.

Name	Sweetness (by weight)	Trade name
Acesulfame potassium	200	Nutrinova
Advantame	20,000	
Alitame	2,000	
Aspartame	160–200	NutraSweet, Equal
Acesulfame	350	Twinsweet
Sodium cyclamate	30	Not Used In USA
Dulcin	250	
Glucin	300	
Neohesperidin dihydrochalcone	1,500	
Neotame	8,000	NutraSweet
P-4000	4,000	
Saccharin	300	Sweet'N Low
Sucralose	600	Kaltame, Splenda

“Histological findings showed that Aspartame 2 and Aspartame 3 caused cyto-architectural changes such as degeneration, monocytes infiltration and necrotic lesions in brain, kidney and liver of rats.”

Journal Of Basic Clinical And Physiological Pharmacology • January 2016

Effects of long-term administration of aspartame on biochemical indices, lipid profile and redox status of cellular system of male rats

Adaramoye OA, Akanni OO.

Abstract

BACKGROUND

Aspartame (N-L-a-aspartyl-L-phenylalanine-1-methyl ester) (ASP) is a synthetic sweetener used in foods and its safety remains controversial. The study was designed to investigate the effects of long-term administration of aspartame on redox status, lipid profile and biochemical indices in tissues of male Wistar rats.

METHODS

Rats were assigned into four groups and given distilled water (control), aspartame at doses of 15 mg/kg (ASP 1), 35 mg/kg (ASP 2) and 70 mg/kg (ASP 3) daily by oral gavage for consecutive 9 weeks.

RESULTS

Administration of ASP 2 and ASP 3 significantly increased the weight of liver and brain, and relative weight of liver of rats. Lipid peroxidation products significantly increased in the kidney, liver and brain of rats at all doses of ASP with concomitant depletion of antioxidant parameters, viz. glutathione-s-transferase, glutathione peroxidase, superoxide dismutase, catalase and reduced glutathione. Furthermore, ASP 2 and ASP 3 significantly increased the levels of gamma glutamyl transferase by 70% and 85%; alanine aminotransferase by 66% and 117%; aspartate amino-transferase by 21% and 48%; urea by 72% and 58% and conjugated bilirubin by 63% and 64%, respectively. Also, ASP 2 and ASP 3 significantly increased the levels of total cholesterol, triglycerides and low-density lipoprotein cholesterol in the rats. Histological findings showed that ASP 2 and ASP 3 caused cyto-architectural changes such as degeneration, monocytes infiltration and necrotic lesions in brain, kidney and liver of rats.

CONCLUSIONS

Aspartame may induce redox and lipid imbalance in rats via mechanism that involves oxidative stress and depletion of glutathione-dependent system.

http://www.ncbi.nlm.nih.gov/pubmed/26247507

American Journal Of Clinical Nutrition • January 2016

Reduced dietary intake of simple sugars alters perceived sweet taste intensity but not perceived pleasantness

Author information

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Abstract

BACKGROUND

Individuals who adhere to reduced-sodium diets come to prefer less salt over time, but it is unclear whether sweet taste perception is modulated by reduced sugar intake.

OBJECTIVE

The objective was to determine how a substantial reduction in dietary intake of simple sugars affects sweetness intensity and pleasantness of sweet foods and beverages.

DESIGN

Healthy men and women aged 21-54 y participated for 5 mo. After the baseline month, 2 subject groups were matched for demographic characteristics, body mass index, and intake of simple sugars. One group (n = 16; 13 of whom completed key experimental manipulations) was randomly assigned to receive a low-sugar diet during the subsequent 3 mo, with instructions to replace 40% of calories from simple sugars with fats, proteins, and complex carbohydrates. The other (control) group (n = 17; 16 of whom completed the study) did not change their sugar intake. During the final month, both groups chose any diet they wished. Each month subjects rated the sweetness intensity and pleasantness of vanilla puddings and raspberry beverages that varied in sucrose concentration.

RESULTS

ANOVA showed no systematic differences between groups in rated sweetness during the baseline or first diet month. During the second diet month, the low-sugar group rated low-sucrose pudding samples as more intense than did the control group (significant group-by-concentration interaction, P = 0.002). During the third diet month, the low-sugar subjects rated both low and high concentrations in puddings as <40% sweeter than did the control group (significant effect of group, P = 0.01). A weaker effect on rated sweetness was obtained for the beverages. Rated pleasantness was not affected for either of the stimuli.

CONCLUSIONS

This experiment provides empirical evidence that changes in consumption of simple sugars influence perceived sweet taste intensity. More work is needed to determine whether sugar intake ultimately shifts preferences for sweet foods and beverages. This trial was registered at clinicaltrials.gov as NCT02090478.

http://www.ncbi.nlm.nih.gov/pubmed/26607941

Critical Reviews In Clinical Laboratory Sciences • February 2016

Sugar consumption, metabolic disease and obesity: The state of the controversy

Author information

By KL Stanhope
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Abstract

The impact of sugar consumption on health continues to be a controversial topic. The objective of this review is to discuss the evidence and lack of evidence that allows the controversy to continue, and why resolution of the controversy is important. There are plausible mechanisms and research evidence that supports the suggestion that consumption of excess sugar promotes the development of cardiovascular disease (CVD) and type 2 diabetes (T2DM) both directly and indirectly. The direct pathway involves the unregulated hepatic uptake and metabolism of fructose, leading to liver lipid accumulation, dyslipidemia, decreased insulin sensitivity and increased uric acid levels. The epidemiological data suggest that these direct effects of fructose are pertinent to the consumption of the fructose-containing sugars, sucrose and high fructose corn syrup (HFCS), which are the predominant added sugars. Consumption of added sugar is associated with development and/or prevalence of fatty liver, dyslipidemia, insulin resistance, hyperuricemia, CVD and T2DM, often independent of body weight gain or total energy intake. There are diet intervention studies in which human subjects exhibited increased circulating lipids and decreased insulin sensitivity when consuming high sugar compared with control diets. Most recently, our group has reported that supplementing the ad libitum diets of young adults with beverages containing 0%, 10%, 17.5% or 25% of daily energy requirement (Ereq) as HFCS increased lipid/lipoprotein risk factors for CVD and uric acid in a dose-response manner. However, un-confounded studies conducted in healthy humans under a controlled, energy-balanced diet protocol that enables determination of the effects of sugar with diets that do not allow for body weight gain are lacking. Furthermore, recent reports conclude that there are no adverse effects of consuming beverages containing up to 30% Ereq sucrose or HFCS, and the conclusions from several meta-analyses suggest that fructose has no specific adverse effects relative to any other carbohydrate. Consumption of excess sugar may also promote the development of CVD and T2DM indirectly by causing increased body weight and fat gain, but this is also a topic of controversy. Mechanistically, it is plausible that fructose consumption causes increased energy intake and reduced energy expenditure due to its failure to stimulate leptin production. Functional magnetic resonance imaging (fMRI) of the brain demonstrates that the brain responds differently to fructose or fructose-containing sugars compared with glucose or aspartame. Some epidemiological studies show that sugar consumption is associated with body weight gain, and there are intervention studies in which consumption of ad libitum high-sugar diets promoted increased body weight gain compared with consumption of ad libitum low- sugar diets. However, there are no studies in which energy intake and weight gain were compared in subjects consuming high or low sugar, blinded, ad libitum diets formulated to ensure both groups consumed a comparable macronutrient distribution and the same amounts of fiber. There is also little data to determine whether the form in which added sugar is consumed, as beverage or as solid food, affects its potential to promote weight gain. It will be very challenging to obtain the funding to conduct the clinical diet studies needed to address these evidence gaps, especially at the levels of added sugar that are commonly consumed. Yet, filling these evidence gaps may be necessary for supporting the policy changes that will help to turn the food environment into one that does not promote the development of obesity and metabolic disease.

http://www.ncbi.nlm.nih.gov/pubmed/26376619

“Artificial sweeteners have been recognized as emerging contaminants due to their wide application, environmental persistence and ubiquitous occurrence. Among them, acesulfame has attracted much attention. After being discharged into the environment, acesulfame undergoes photolysis naturally. However, acesulfame photodegradation behavior and identity of its transformation products, critical to understanding acesulfame’s environmental impact, have not been thoroughly investigated. The present study aimed to fill this knowledge gap ... Our results show six new transformation products that have not been previously identified. The molecular structures and transformation pathways were proposed. Further embryotoxicity tests showed that acesulfame transformation products at the *low g L(-1) level produced significant adverse effects in tail detachment, heart rate, hatching rate and survival rate during fish embryo development ... the increased toxicity of acesulfame ... and the fact that the accumulation of acesulfame transformation products is increasingly likely make acesulfame contamination even more important.”

Water Research • February 2016

Photocatalytic transformation of acesulfame: Transformation products identification and embryotoxicity study

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Abstract

Artificial sweeteners have been recognized as emerging contaminants due to their wide application, environmental persistence and ubiquitous occurrence. Among them, acesulfame has attracted much attention. After being discharged into the environment, acesulfame undergoes photolysis naturally. However, acesulfame photodegradation behavior and identity of its transformation products, critical to understanding acesulfame’s environmental impact, have not been thoroughly investigated. The present study aimed to fill this knowledge gap by a laboratory simulation study in examining acesulfame transformation products and pathways under UV-C photolysis in the presence of TiO2. Photodegradation products of acesulfame were isolated and analyzed using the LC-IM-QTOF-MS coupled with LC Ion Trap MS in the MS(n) mode. Our results show six new transformation products that have not been previously identified. The molecular structures and transformation pathways were proposed. Further embryotoxicity tests showed that acesulfame transformation products at the low g L(-1) level produced significant adverse effects in tail detachment, heart rate, hatching rate and survival rate during fish embryo development. The identification of additional transformation products with proposed transformation pathways of acesulfame, the increased toxicity of acesulfame after photolysis, and the fact that the accumulation of acesulfame transformation products is increasingly likely make acesulfame contamination even more important. Water resource control agencies need to consider legislation regarding acesulfame and other artificial sweeteners, while further studies are carried out, in order to protect the safety of this most vital resource.

http://www.ncbi.nlm.nih.gov/pubmed/26630044

“The findings suggest that Noncaloric Artificial Sweeteners disturb the circadian sleep-wake cycle and cause behavioral inactivity in mice.”

Nutrition • March 2016

Moderately high doses of the artificial sweetener saccharin potentially induce sleep disorders in mice

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Abstract

OBJECTIVES
Caloric sweeteners such as sugar and honey are replaced in thousands of food products by noncaloric artificial sweeteners (NASs).
The aim of the present study was to determine the effects of chronic NAS intake on circadian sleep regulation.
METHODS
Circadian rhythms of sleep and locomotor activity were evaluated in mice after consumption of drinking water containing 0.1% (w/v) saccharin for 2 wk.
RESULTS
The intake of saccharin ad libitum significantly reduced wakefulness and increased non-rapid eye movement sleep during the first half of the active (dark) phase, whereas wakefulness was significantly increased at the start of the sleep phase. Saccharin consumption obviously reduced spontaneous activity during the first half of the dark period.
CONCLUSIONS
The findings suggest that NASs disturb the circadian sleep-wake cycle and cause behavioral inactivity in mice.

http://www.ncbi.nlm.nih.gov/pubmed/27189909

“There is a striking congruence between results from animal research and a number of large-scale, long-term observational studies in humans, in finding significantly increased weight gain, adiposity, incidence of obesity, cardiometabolic risk, and even total mortality among individuals with chronic, daily exposure to low-calorie sweeteners - and these results are troubling.”

Physiology And Behavior • April 2016

Low-calorie sweetener use and energy balance: Results from experimental studies in animals, and large-scale prospective studies in humans

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Abstract

For more than a decade, pioneering animal studies conducted by investigators at Purdue University have provided evidence to support a central thesis: that the uncoupling of sweet taste and caloric intake by low-calorie sweeteners (LCS) can disrupt an animal's ability to predict the metabolic consequences of sweet taste, and thereby impair the animal's ability to respond appropriately to sweet-tasting foods. These investigators' work has been replicated and extended internationally. There now exists a body of evidence, from a number of investigators, that animals chronically exposed to any of a range of LCSs - including saccharin, sucralose, acesulfame potassium, aspartame, or the combination of erythritol+aspartame - have exhibited one or more of the following conditions: increased food consumption, lower post-prandial thermogenesis, increased weight gain, greater percent body fat, decreased GLP-1 release during glucose tolerance testing, and significantly greater fasting glucose, glucose area under the curve during glucose tolerance testing, and hyperinsulinemia, compared with animals exposed to plain water or - in many cases - even to calorically-sweetened foods or liquids. Adverse impacts of LCS have appeared diminished in animals on dietary restriction, but were pronounced among males, animals genetically predisposed to obesity, and animals with diet-induced obesity. Impacts have been especially striking in animals on high-energy diets: diets high in fats and sugars, and diets which resemble a highly-processed 'Western' diet, including trans-fatty acids and monosodium glutamate. These studies have offered both support for, and biologically plausible mechanisms to explain, the results from a series of large-scale, long-term prospective observational studies conducted in humans, in which longitudinal increases in weight, abdominal adiposity, and incidence of overweight and obesity have been observed among study participants who reported using diet sodas and other LCS-sweetened beverages daily or more often at baseline. Furthermore, frequent use of diet beverages has been associated prospectively with increased long-term risk and/or hazard of a number of cardiometabolic conditions usually considered to be among the sequelae of obesity: hypertension, metabolic syndrome, diabetes, depression, kidney dysfunction, heart attack, stroke, and even cardiovascular and total mortality. Reverse causality does not appear to explain fully the increased risk observed across all of these studies, the majority of which have included key potential confounders as covariates. These have included body mass index or waist circumference at baseline; total caloric intake and specific macronutrient intake; physical activity; smoking; demographic and other relevant risk factors; and/or family history of disease. Whether non-LCS ingredients in diet beverages might have independently increased the weight gain and/or cardiometabolic risk observed among frequent consumers of LCS-sweetened beverages deserves further exploration. In the meantime, however, there is a striking congruence between results from animal research and a number of large-scale, long-term observational studies in humans, in finding significantly increased weight gain, adiposity, incidence of obesity, cardiometabolic risk, and even total mortality among individuals with chronic, daily exposure to low-calorie sweeteners - and these results are troubling.

http://www.ncbi.nlm.nih.gov/pubmed/27129676

“The results of this study demonstrated that that carbonated soft drinks induced oxidative stress and altered the expression of certain genes that are associated with the brain activity and thus should be consumed with caution.”

Molecular Medicine Reports • April 2016

Carbonated soft drinks induce oxidative stress and alter the expression of certain genes in the brains of Wistar rats

Author information

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Abstract

In Saudi Arabia, the consumption of carbonated soft drinks is common and often occurs with each meal. Carbonated soft drink consumption has been shown to exhibit effects on the liver, kidney and bone. However, the effects of these soft drinks on brain activity have not been widely examined, particularly at the gene level. Therefore, the current study was conducted with the aim of evaluating the effects of chronic carbonated soft drink consumption on oxidative stress, brain gene biomarkers associated with aggression and brain histology. In total, 40 male Wistar rats were divided into four groups: Group 1 served as a control and was provided access to food and water ad libitum; and groups 2-4 were given free access to food and carbonated soft drinks only (Cola for group 2, Pepsi for group 3 and 7-UP for group 4). Animals were maintained on these diets for 3 consecutive months. Upon completion of the experimental period, animals were sacrificed and serological and histopathological analyses were performed on blood and tissues samples. Reverse transcription-polymerase chain reaction was used to analyze alterations in gene expression levels. Results revealed that carbonated soft drinks increased the serum levels of malondialdehyde (MDA). Carbonated soft drinks were also observed to downregulate the expression of antioxidants glutathione reductase (GR), catalase and glutathione peroxidase (GPx) in the brain when compared with that in the control rats. Rats administered carbonated soft drinks also exhibited decreased monoamine oxidase A (MAO-A) and acetylcholine esterase (AChE) serum and mRNA levels in the brain. In addition, soft drink consumption upregulated mRNA expression of dopamine D2 receptor (DD2R), while 5-hydroxytryptamine transporter (5-HTT) expression was decreased. However, following histological examination, all rats had a normal brain structure. The results of this study demonstrated that that carbonated soft drinks induced oxidative stress and altered the expression of certain genes that are associated with the brain activity and thus should be consumed with caution.

http://www.ncbi.nlm.nih.gov/pubmed/26936207

“These findings highlight the potential for steviol to act as a potential endocrine disruptor.”

Molecular And Cellular Endocrinology • May 2016

In vitro bioassay investigations of the endocrine disrupting potential of steviol glycosides and their metabolite steviol, components of the natural sweetener Stevia

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Abstract

The food industry is moving towards the use of natural sweeteners such as those produced by Stevia rebaudiana due to the number of health and safety concerns surrounding artificial sweeteners. Despite the fact that these sweeteners are natural; they cannot be assumed safe. Steviol glycosides have a steroidal structure and therefore may have the potential to act as an endocrine disruptor in the body. Reporter gene assays (RGAs), H295R steroidogenesis assay and Ca(2+) fluorimetry based assays using human sperm cells have been used to assess the endocrine disrupting potential of two steviol glycosides: stevioside and rebaudioside A, and their metabolite steviol. A decrease in transcriptional activity of the progestagen receptor was seen following treatment with 25,000 ng/ml steviol in the presence of progesterone (157 ng/ml) resulting in a 31% decrease in progestagen response ($p=<0.01$). At the level of steroidogenesis, the metabolite steviol (500-25,000 ng/ml) increased progesterone production significantly by 2.3 fold when exposed to 10,000 ng/ml ($p=<0.05$) and 5 fold when exposed to 25,000 ng/ml ($p=<0.001$). Additionally, steviol was found to induce an agonistic response on CatSper, a progesterone receptor of sperm, causing a rapid influx of Ca(2+). The response was fully inhibited using a specific CatSper inhibitor. These findings highlight the potential for steviol to act as a potential endocrine disruptor.

http://www.ncbi.nlm.nih.gov/pubmed/26965840

Current Opinions In Behavioral Science • June 2016

Not-so-healthy sugar substitutes?

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Abstract

“**Replacing sugar-sweetened beverages with diet soft drinks containing sugar substitutes that provide few or no calories has been suggested as one strategy for promoting improved public health outcomes. However, current scientific evidence indicates that routine consumption of beverages with non-nutritive sweeteners not only fails to prevent disease, but is associated with increases in risks for the same health outcomes associated with sugar-sweetened beverages, including type 2 diabetes, cardiovascular disease, hypertension and stroke.** Results from pre-clinical studies have provided plausible biological mechanisms that could promote these counterintuitive negative health effects of artificial sweeteners. Taken together, scientific studies currently indicate that public health will be improved by reducing intake of all sweeteners, both caloric and non-caloric.”

http://www.ncbi.nlm.nih.gov/pubmed/27135048

“Our findings suggest that high levels of sugar-sweetened carbonated beverage consumption are associated with a higher prevalence and degree of coronary artery calcium in asymptomatic adults without a history of cardiovascular disease, cancer, or diabetes.”

American Heart Journal • July 2016

Sugar-sweetened carbonated beverage consumption and coronary artery calcification in asymptomatic men and women

Author information

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Abstract

BACKGROUND

Sugar-sweetened carbonated beverage consumption has been linked to obesity, metabolic syndrome, type 2 diabetes, and clinically manifest coronary heart disease, but its association with subclinical coronary heart disease remains unclear. We investigated the relationship between sugar-sweetened carbonated beverage consumption and coronary artery calcium (CAC) in a large study of asymptomatic men and women.

METHODS

This was a cross-sectional study of 22,210 adult men and women who underwent a comprehensive health screening examination between 2011 and 2013 (median age 40 years). Sugar-sweetened carbonated beverage consumption was assessed using a validated food frequency questionnaire, and CAC was measured by cardiac computed tomography. Multivariable-adjusted CAC score ratios and 95% CIs were estimated from robust Tobit regression models for the natural logarithm (CAC score +1).

RESULTS

The prevalence of detectable CAC (CAC score >0) was 11.7% (n = 2,604). After adjustment for age; sex; center; year of screening examination; education level; physical activity; smoking; alcohol intake; family history of cardiovascular disease; history of hypertension; history of hypercholesterolemia; and intake of total energy, fruits, vegetables, and red and processed meats, only the highest category of sugar-sweetened carbonated beverage consumption was associated with an increased CAC score compared with the lowest consumption category. The multivariable-adjusted CAC ratio comparing participants who consumed ≥5 sugar-sweetened carbonated beverages per week with nondrinkers was 1.70 (95% CI, 1.03-2.81). This association did not differ by clinical subgroup, including participants at low cardiovascular risk.

CONCLUSION

Our findings suggest that high levels of sugar-sweetened carbonated beverage consumption are associated with a higher prevalence and degree of CAC in asymptomatic adults without a history of cardiovascular disease, cancer, or diabetes.

http://www.ncbi.nlm.nih.gov/pubmed/27297845

“To our knowledge, we provide the first human evidence that maternal consumption of artificial sweeteners during pregnancy may influence infant BMI. Given the current epidemic of childhood obesity and widespread use of artificial sweeteners, further research is warranted to confirm our findings and investigate the underlying biological mechanisms, with the ultimate goal of informing evidence-based dietary recommendations for pregnant women.”

JAMA Pediatrics • July 2016

Association Between Artificially Sweetened Beverage Consumption During Pregnancy and Infant Body Mass Index

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Abstract

IMPORTANCE

The consumption of artificial sweeteners has increased substantially in recent decades, including among pregnant women. Animal studies suggest that exposure to artificial sweeteners in utero may predispose offspring to develop obesity; however, to our knowledge, this has never been studied in humans.

OBJECTIVE

To determine whether maternal consumption of artificially sweetened beverages during pregnancy is associated with infant body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]).

DESIGN, SETTING, AND PARTICIPANTS

This cohort study included 3033 mother-infant dyads from the Canadian Healthy Infant Longitudinal Development (CHILD) Study, a population-based birth cohort that recruited healthy pregnant women from 2009 to 2012. Women completed dietary assessments during pregnancy, and their infants’ BMI was measured at 1 year of age (n=2686; 89% follow-up). Statistical analysis for this study used data collected after the first year of follow-up, which was completed in October 2013. The data analysis was conducted in August 2015.

EXPOSURES

Maternal consumption of artificially sweetened beverages and sugar-sweetened beverages during pregnancy, determined by a food frequency questionnaire.

MAIN OUTCOMES AND MEASURES

Infant BMI z score and risk of overweight at 1 year of age, determined from objective anthropometric measurements and defined according to World Health Organization reference standards.

RESULTS

The mean (SD) age of the 3033 pregnant women was 32.4 (4.7) years, and their mean (SD) BMI was 24.8 (5.4). The mean (SD) infant BMI z score at 1 year of age was 0.19 (1.05), and 5.1% of infants were overweight. More than a quarter of women (29.5%) consumed artificially sweetened beverages during pregnancy, including 5.1% who reported daily consumption. Compared with no consumption, daily consumption of artificially sweetened beverages was associated with a 0.20-unit increase in infant BMI z score (adjusted 95% CI, 0.02-0.38) and a 2-fold higher risk of infant overweight at 1 year of age (adjusted odds ratio, 2.19; 95% CI, 1.23-3.88). These effects were not explained by maternal BMI, diet quality, total energy intake, or other obesity risk factors. There were no comparable associations for sugar-sweetened beverages.

CONCLUSIONS AND RELEVANCE

To our knowledge, we provide the first human evidence that maternal consumption of artificial sweeteners during pregnancy may influence infant BMI. Given the current epidemic of childhood obesity and widespread use of artificial sweeteners, further research is warranted to confirm our findings and investigate the underlying biological mechanisms, with the ultimate goal of informing evidence-based dietary recommendations for pregnant women.

http://www.ncbi.nlm.nih.gov/pubmed/27159792

“These results suggest that aspartame and saccharin could be toxic to the human circulation system as well as embryonic development via impairment of lipoprotein function.”

Cardiovascular Toxicology • January 2015

Modified high-density lipoproteins by artificial sweetener, aspartame, and saccharin, showed loss of anti-atherosclerotic activity and toxicity in zebrafish

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Abstract

Safety concerns have been raised regarding the association of chronic consumption of artificial sweeteners (ASs) with metabolic disorders, especially in the heart and brain. There has been no information on the in vivo physiological effects of AS consumption in lipoprotein metabolism. High-dosage treatment (final 25, 50, and 100 mM) with AS (aspartame, acesulfame K, and saccharin) to human high-density lipoprotein (HDL) induced loss of antioxidant ability along with elevated atherogenic effects. Aspartame-treated HDL3 (final 100 mM) almost all disappeared due to putative proteolytic degradation. Aspartame- and saccharin-treated HDL3 showed more enhanced cholesteryl ester transfer activity, while their antioxidant ability was disappeared. Microinjection of the modified HDL3 exacerbated the inflammatory death in zebrafish embryos in the presence of oxLDL. These results show that AS treatment impaired the beneficial functions of HDL, resulting in loss of antioxidant and anti-atherogenic activities. These results suggest that aspartame and saccharin could be toxic to the human circulation system as well as embryonic development via impairment of lipoprotein function.

http://www.ncbi.nlm.nih.gov/pubmed/25142179

“While they are considered safe, there is increasing controversy regarding their potential ability to promote metabolic derangements in some humans. We recently demonstrated that NAS consumption could induce glucose intolerance in mice and distinct human subsets ...”

Gut Microbes • April 2015

Non-caloric artificial sweeteners and the microbiome: findings and challenges

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Abstract

Non-caloric artificial sweeteners (NAS) are common food supplements consumed by millions worldwide as means of combating weight gain and diabetes, by retaining sweet taste without increasing caloric intake. While they are considered safe, there is increasing controversy regarding their potential ability to promote metabolic derangements in some humans. We recently demonstrated that NAS consumption could induce glucose intolerance in mice and distinct human subsets, by functionally altering the gut microbiome. In this commentary, we discuss these findings in the context of previous and recent works demonstrating the effects of NAS on host health and the microbiome, and the challenges and open questions that need to be addressed in understanding the effects of NAS consumption on human health.

http://www.ncbi.nlm.nih.gov/pubmed/25831243

“In addition to a significant reduction in the body weight, the Artificial Sweetener-treated groups displayed elevated enzymes activities, lowered antioxidants values, and histological changes reflecting the hepatotoxic effect of aspartame and saccharin. Moreover, the overexpression of the key oncogene (h-Ras) and the downregulation of the tumor suppressor gene (P27) in all treated rat groups may indicate a potential risk of liver carcinogenesis, particularly on long-term exposure.”

International Journal Of Immunopathology And Pharmacology • June 2015

Impact of aspartame and saccharin on the rat liver: Biochemical, molecular, and histological approach

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Abstract

The current work was undertaken to settle the debate about the toxicity of artificial sweeteners (AS), particularly aspartame and saccharin. Twenty-five, 7-week-old male Wistar albino rats with an average body weight of 101 ± 4.8 g were divided into a control group and four experimental groups (n = 5 rats). The first and second experimental groups received daily doses equivalent to the acceptable daily intake (ADI) of aspartame (250 mg/Kg BW) and four-fold ADI of aspartame (1000 mg/Kg BW). The third and fourth experimental groups received daily doses equivalent to ADI of saccharin (25 mg/Kg BW) and four-fold ADI of saccharin (100 mg/Kg BW). The experimental groups received the corresponding sweetener dissolved in water by oral route for 8 weeks. The activities of enzymes relevant to liver functions and antioxidants were measured in the blood plasma. Histological studies were used for the evaluation of the changes in the hepatic tissues. The gene expression levels of the key oncogene (h-Ras) and the tumor suppressor gene (P27) were also evaluated. In addition to a significant reduction in the body weight, the AS-treated groups displayed elevated enzymes activities, lowered antioxidants values, and histological changes reflecting the hepatotoxic effect of aspartame and saccharin. Moreover, the overexpression of the key oncogene (h-Ras) and the downregulation of the tumor suppressor gene (P27) in all treated rat groups may indicate a potential risk of liver carcinogenesis, particularly on long-term exposure.

http://www.ncbi.nlm.nih.gov/pubmed/26015492

“Long-term consumption of sugar substitutes aggravated cerebral ischemic injury in mice ...”

Stroke • June 2015

Dietary intake of sugar substitutes aggravates cerebral ischemic injury and impairs endothelial progenitor cells in mice

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Abstract

BACKGROUND AND PURPOSE

In our current food supply, sugar substitutes are widely used in beverages and other food products. However, there is limited information about the link between dietary consumption of sugar substitutes and stroke to date. This study sought to determine the effect of various sugar substitutes on the cerebral ischemic injury and endothelial progenitor cells, which have been implicated to play an important role in vascular repair and revascularization in ischemic brain tissues, in mice.

METHODS

After treatment with sucrose and various sugar substitutes (the doses are in the range of corresponding acceptable daily intake levels) and vehicle for 6 weeks, mice were subjected to permanent left middle cerebral artery occlusion, and the infarct volumes, angiogenesis, and neurobehavioral outcomes were determined. In addition, the number and function of endothelial progenitor cells were also examined.

RESULTS

After long-term treatment with fructose, erythritol (sugar alcohols), acesulfame K (artificial sweeteners), or rebaudioside A (rare sugars), the cerebral ischemic injury (both infarct volumes and neurobehavioral outcomes) was significantly aggravated, angiogenesis in ischemic brain was reduced, and endothelial progenitor cell function was impaired in mice compared with control. However, the similar impairments were not found in sucrose (with the same dose as fructose’s)-treated mice.

CONCLUSIONS

Long-term consumption of sugar substitutes aggravated cerebral ischemic injury in mice, which might be partly attributed to the impairment of endothelial progenitor cells and the reduction of angiogenesis in ischemic brain. This result implies that dietary intake of sugar substitutes warrants further attention in daily life.

http://www.ncbi.nlm.nih.gov/pubmed/25908458

“These results provide mechanistic support for the epidemiologic evidence that the risk of cardiovascular mortality is positively associated with consumption of increasing amounts of added sugars.”

American Journal Of Clinical Nutrition • June 2015

A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults

Author information

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Abstract

BACKGROUND

National Health and Nutrition Examination Survey data show an increased risk of cardiovascular disease (CVD) mortality with an increased intake of added sugar.

OBJECTIVE

We determined the dose-response effects of consuming beverages sweetened with high-fructose corn syrup (HFCS) at zero, low, medium, and high proportions of energy requirements (Ereq) on circulating lipid/lipoprotein risk factors for CVD and uric acid in adults [age: 18-40 y; body mass index (in kg/m(2)): 18-35].

DESIGN

We conducted a parallel-arm, nonrandomized, double-blinded intervention study in which adults participated in 3.5 inpatient days of baseline testing at the University of California Davis Clinical and Translational Science Center’s Clinical Research Center. Participants then consumed beverages sweetened with HFCS at 0% (aspartame sweetened, n = 23), 10% (n = 18), 17.5% (n = 16), or 25% (n = 28) of Ereq during 13 outpatient days and during 3.5 inpatient days of intervention testing at the research center. We conducted 24-h serial blood collections during the baseline and intervention testing periods.

RESULTS

Consuming beverages containing 10%, 17.5%, or 25% Ereq from HFCS produced significant linear dose-response increases of lipid/lipoprotein risk factors for CVD and uric acid: postprandial triglyceride (0%: 0 ± 4; 10%: 22 ± 8; 17.5%: 25 ± 5: 25%: 37 ± 5 mg/dL, mean of Δ ± SE, $P < 0.0001$ effect of HFCS-dose), fasting LDL cholesterol (0%: -1.0 ± 3.1; 10%: 7.4 ± 3.2; 17.5%: 8.2 ± 3.1; 25%: 15.9 ± 3.1 mg/dL, $P < 0.0001$), and 24-h mean uric acid concentrations (0%: -0.13 ± 0.07; 10%: 0.15 ± 0.06; 17.5%: 0.30 ± 0.07; 25%: 0.59 ± 0.09 mg/dL, $P < 0.0001$). Compared with beverages containing 0% HFCS, all 3 doses of HFCS-containing beverages increased concentrations of postprandial triglyceride, and the 2 higher doses increased fasting and/or postprandial concentrations of non-HDL cholesterol, LDL cholesterol, apolipoprotein B, apolipoprotein CIII, and uric acid.

CONCLUSIONS

Consuming beverages containing 10%, 17.5%, or 25% Ereq from HFCS produced dose-dependent increases in circulating lipid/lipoprotein risk factors for CVD and uric acid within 2 wk. These results provide mechanistic support for the epidemiologic evidence that the risk of cardiovascular mortality is positively associated with consumption of increasing amounts of added sugars. This trial was registered at clinicaltrials.gov as NCT01103921.

http://www.ncbi.nlm.nih.gov/pubmed/25904601

“These experimental findings support a metabolic-brain negative feedback pathway that is affected by sugar and may make some people under stress more hooked on sugar and possibly more vulnerable to obesity and its related conditions.”

Journal Of Clinical Endocrinology And Metabolism • June 2015

Excessive Sugar Consumption May Be a Difficult Habit to Break: A View From the Brain and Body

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Abstract

CONTEXT

Sugar overconsumption and chronic stress are growing health concerns because they both may increase the risk for obesity and its related diseases. Rodent studies suggest that sugar consumption may activate a glucocorticoid-metabolic-brain-negative feedback pathway, which may turn off the stress response and thereby reinforce habitual sugar overconsumption.

OBJECTIVE

The objective of the study was to test our hypothesized glucocorticoid-metabolic-brain model in women consuming beverages sweetened with either aspartame of sucrose.

RESULTS

Compared with aspartame, sucrose consumption was associated with significantly higher activity in the left hippocampus (P = .001). Sucrose, but not aspartame, consumption associated with reduced (P = .024) stress-induced cortisol. The sucrose group also had a lower reactivity to naltrexone, significantly (P = .041) lower nausea, and a trend (P = .080) toward lower cortisol.

CONCLUSION

These experimental findings support a metabolic-brain-negative feedback pathway that is affected by sugar and may make some people under stress more hooked on sugar and possibly more vulnerable to obesity and its related conditions.

http://www.ncbi.nlm.nih.gov/pubmed/25879513

“Aspartame and saccharin also decreased the survival and behaviour of adult flies and may be toxic to (or contribute to poor nutrition in) B. dorsalis. These sweeteners could therefore be developed as additive ingredients in baits [to kill rodents].”

Pest Management Science • July 2015

Effect of sweeteners on the survival and behaviour of Bactrocera dorsalis (Hendel) (Diptera: Tephritidae)

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Abstract

BACKGROUND

The oriental fruit fly Bactrocera dorsalis (Hendel) (Diptera: Tephritidae) causes serious damage that affects fruit production. Chemical insecticides have been widely used for the prevention and control of this destructive pest. However, the resistance of B. dorsalis to these compounds has become a serious problem. This study tested six sweeteners for their toxicity to B. dorsalis.

RESULTS:

B. dorsalis fed on erythritol, aspartame and saccharin exhibited significantly higher mortality than those fed on sucrose. Flies fed on erythritol died faster than did the control flies (water). However, no dose-dependent effects were observed at the concentrations tested. These three sweeteners decreased the climbing ability of B. dorsalis. Notably, adults fed on saccharin exhibited significantly decreased climbing ability after 12 h compared with those fed on sucrose. Additionally, these three sweeteners had a negative effect on the frequency and duration of the flies' behaviour patterns (flying, walking, grooming and inactivity). Saccharin not only induced a marked reduction in the frequency of flights and walks but also induced decreases in the time spent flying and walking and increases in inactivity compared with sucrose. Erythritol induced a reduction in movement and increased the time spent inactive compared with the control and other treatments.

CONCLUSION:

Three sweeteners had significant negative effects on the survival of B. dorsalis. Erythritol was toxic to B. dorsalis. Aspartame and saccharin also decreased the survival and behaviour of adult flies and may be toxic to (or contribute to poor nutrition in) B. dorsalis. These sweeteners could therefore be developed as additive ingredients in baits.

http://www.ncbi.nlm.nih.gov/pubmed/26177595

“Saccharin, sucralose, and acesulfame-potassium were present in 65% of participants’ milk samples, whereas aspartame was not detected. These data indicate that non-nutritive sweeteners are frequently ingested by nursing infants, and thus prospective clinical studies are necessary to determine whether early non-nutritive sweetener exposure via breast milk may have clinical implications.”

Journal Of Toxicology And Environmental Health, Part A • August 2015

Nonnutritive Sweeteners in Breast Milk

Author information

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Abstract

Nonnutritive sweeteners (NNS), including saccharin, sucralose, aspartame, and acesulfame-potassium, are commonly consumed in the general population, and all except for saccharin are considered safe for use during pregnancy and lactation. Sucralose (Splenda) currently holds the majority of the NNS market share and is often combined with acesulfame-potassium in a wide variety of foods and beverages. To date, saccharin is the only NNS reported to be found in human breast milk after maternal consumption, while there is no apparent information on the other NNS. Breast milk samples were collected from 20 lactating volunteers, irrespective of their habitual NNS intake. Saccharin, sucralose, and acesulfame-potassium were present in 65% of participants’ milk samples, whereas aspartame was not detected. These data indicate that NNS are frequently ingested by nursing infants, and thus prospective clinical studies are necessary to determine whether early NNS exposure via breast milk may have clinical implications.

http://www.ncbi.nlm.nih.gov/pubmed/26267522

BMJ • August 2015

Fetal exposure to dietary carcinogens and risk of childhood cancer: what the NewGeneris project tells us

Author Information

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Jos Kleinjans and colleagues summarise the evidence from a European study using biomarkers to assess how maternal diet affects the child

Abstract

Cancer in childhood is rare. Globally, there are around 175 000 new cancer cases a year among children aged 0-14 years. However, in Europe, since the 1950s the incidence of cancer in this age group has increased by about 1% a year, with leukaemia, brain tumours, and lymphomas accounting for most cases. The increases in incidence of lymphoid leukaemia, in particular, are more apparent in European than in Asian or African children. The development of childhood cancer thus seems to be affected by both genetic and environmental factors. Given that the highest incidences of childhood leukaemia are reported in children younger than 6-7 years, that the latency period of leukaemia in children is relatively short, and that adverse genetic events in utero have been shown to give rise to leukaemia in childhood, we hypothesised that fetal exposure to environmental carcinogens may be an underlying cause. Diet is an important source of carcinogenic compounds because of the accumulation of environmental carcinogens within the food chain (dioxins, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs)), as well as of formation of carcinogens such as PAHs, heterocyclic amines, and acrylamide during baking, frying, and grilling of food. The New Generis (Newborns and Genotoxic Exposure Risks) project therefore set out to investigate whether intake of dietary carcinogens by the pregnant mother leads to exposures of the fetus and initiates adverse biological responses that can induce cancer in later childhood.

Investigation of this hypothesis in an epidemiological study would require a huge sample size because of the relatively low incidence of childhood cancer (about 140 cases per million children). Case-control studies have been informative but also have limitations.

“Key messages:

- An estimated 175,000 new cancer cases occur globally among children aged 0-14
- The fetus is exposed to dietary carcinogens consumed by the mother during pregnancy
- Exposure of the fetus causes perturbations of the molecular pathways linked with markers of carcinogenicity
- Genetic polymorphisms and male sex may predispose to susceptibility to carcinogen exposure before birth
- This increases risks of developing leukaemia, in particular
- Fetal exposure to dietary carcinogens may also affect birth weight and cause immune suppression”

http://www.bmj.com/content/351/bmj.h4501.long

“Aspartame exposure resulted in detectable methanol even after 24 hours. Methanol and its metabolites may be responsible for the generation of oxidative stress in brain regions. The observed alteration in aspartame fed animals may be due to its metabolite methanol and elevated formate.”

Journal Of Biomedical Research • September 2015

Acute effect of aspartame-induced oxidative stress in Wistar albino rat brain

Author information

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Abstract

The present study was carried out to investigate the acute effect of aspartame on oxidative stress in the Wistar albino rat brain. We sought to investigate whether acute administration of aspartame (75 mg/kg) could release methanol and induce oxidative stress in the rat brain 24 hours after administration. To mimic human methanol metabolism, methotrexate treated rats were used to study aspartame effects. Wistar strain male albino rats were administered with aspartame orally as a single dose and studied along with controls and methotrexate treated controls. Blood methanol and formate level were estimated after 24 hours and rats were sacrificed and free radical changes were observed in discrete regions by assessing the scavenging enzymes, reduce dglutathione (GSH), lipid peroxidation and protein thiol levels. There was a significant increase in lipid peroxidation levels, superoxide dismutase activity (SOD), glutathione peroxidase levels (GPx), and catalase activity (CAT) with a significant decrease in GSH and protein thiol. Aspartame exposure resulted in detectable methanol even after 24 hours. Methanol and its metabolites may be responsible for the generation of oxidative stress in brain regions. The observed alteration in aspartame fed animals may be due to its metabolite methanol and elevated formate. The elevated free radicals due to methanol induced oxidative stress.

http://www.ncbi.nlm.nih.gov/pubmed/26445572

“We found that the ranking of developmental toxicity was Saccharin > Caffeine > Aspartame > Sucrose, and there was a cumulative effect when Caffeine was combined with the sweeteners.”

Springerplus • September 2015

Assessing developmental toxicity of caffeine and sweeteners in medaka (Oryzias latipes)

Author information

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Abstract

The use of artificial sweeteners (ASWs) has increased and become more widespread, and consequently ASWs have appeared in aquatic environments around the world. However, their safety to the health of humans and wildlife remains inconclusive. In this study, using medaka embryos (Oryzias latipes), we investigated developmental toxicity of aspartame (ASP) and saccharin (SAC). Since ASWs are often consumed with caffeine (CAF) and CAF with sucrose (SUC), we tested biological activities of these four substances and the mixtures of CAF with each sweetener. The embryos were exposed to ASP at 0.2 and 1.0 mM, SAC at 0.005 and 0.050 mM, CAF at 0.05 and 0.5 mM, or SUC at 29 and 146 mM, starting from less than 5 h post fertilization until hatch. Control embryos were treated with embryo solution only. Several endpoints were used to evaluate embryonic development. Some of the hatchlings were also tested for anxiety-like behavior with the white preference test. The results showed that all four substances and the mixtures of CAF with the sweeteners affected development. The most sensitive endpoints were the heart rate, eye density, and hatchling body length. The hatchlings of several treatment groups also exhibited anxiety-like behavior. We then used the Integrated Biological Response (IBR) as an index to evaluate the overall developmental toxicity of the substances. We found that the ranking of developmental toxicity was SAC > CAF > ASP > SUC, and there was a cumulative effect when CAF was combined with the sweeteners.

Full text, graphs and charts with 42 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4562911/

“Sucralose and sodium saccharin seemed to elicit the greatest degree of DNA fragmentation of all the sweeteners tested in all the cell lines used. Morphological cell alterations, cell viability and DNA fragmentation seemed to be more in the colon cancer cells.”

Drug Chemistry And Toxicology • October 2015

The effect of five artificial sweeteners on Caco-2, HT-29 and HEK-293 cells

Author information

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Abstract

CONTEXT

Artificial sweeteners (AS) have been associated with tumor development (including colon cancer) in both animals and humans although evidence has been conflicting.

OBJECTIVES

Additional research was thus conducted by studying the effects of 5 AS on the morphology, cell proliferation and DNA in cells by utilizing Caco-2, HT-29 (colon) and HEK-293 (kidney) cell lines.

RESULTS

Cells became flatter and less well defined at higher AS concentrations (>10 mM). At concentrations >10 mM, decreased cell viability was noted with both increasing concentration and increasing incubation time for all cell lines tested. In general, HEK-293 cells seemed to be less affected then the colon cancer cells. Sucralose and sodium saccharin seemed to elicit the greatest degree of DNA fragmentation of all the sweeteners tested in all the cell lines used.

DISCUSSION

Morphological cell alterations, cell viability and DNA fragmentation seemed to be more in the colon cancer cells.

CONCLUSIONS

Further studies have to be performed to clarify mechanisms involved causing these alterations in mammalian cells.

http://www.ncbi.nlm.nih.gov/pubmed/25317478

“... a scientific consensus has emerged suggesting that consumption of sugar-sweetened products, especially beverages, is casually linked to increases in risk of chronic, debilitating diseases including type 2 diabetes, cardiovascular disease, hypertension and stroke.”

Appetite • October 2015

Artificial sweeteners are not the answer to childhood obesity

Author information

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Abstract

While no single factor is responsible for the recent, dramatic increases in overweight and obesity, a scientific consensus has emerged suggesting that consumption of sugar-sweetened products, especially beverages, is casually linked to increases in risk of chronic, debilitating diseases including type 2 diabetes, cardiovascular disease, hypertension and stroke. One approach that might be beneficial would be to replace sugar-sweetened items with products manufactured with artificial sweeteners that provide sweet tastes but with fewer calories. Unfortunately, evidence now indicates that artificial sweeteners are also associated with increased risk of the same chronic diseases linked to sugar consumption. Several biologically plausible mechanisms may explain these counterintuitive negative associations. For example, artificial sweeteners can interfere with basic learning processes that serve to anticipate the normal consequences of consuming sugars, leading to overeating, diminished release of hormones such as GLP-1, and impaired blood glucose regulation. In addition, artificial sweeteners can alter gut microbiota in rodent models and humans, which can also contribute to impaired glucose regulation. Use of artificial sweeteners may also be particularly problematic in children since exposure to hyper-sweetened foods and beverages at young ages may have effects on sweet preferences that persist into adulthood. Taken as a whole, current evidence suggests that a focus on reducing sweetener intake, whether the sweeteners are caloric or non-caloric, remains a better strategy for combating overweight and obesity than use of artificial sweeteners.

http://www.ncbi.nlm.nih.gov/pubmed/25828597

Environmental Science And Pollution Research International • November 2015

Antibiotics and sweeteners in the aquatic environment: biodegradability, formation of phototransformation products, and in vitro toxicity

Author information

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Abstract

In the present study, in vitro toxicity as well as biopersistence and photopersistence of four artificial sweeteners (acesulfame, cyclamate, saccharine, and sucralose) and five antibiotics (levofloxacin, lincomycin, linezolid, marbofloxacin, and sarafloxacin) and of their phototransformation products (PTPs) were investigated. Furthermore, antibiotic activity was evaluated after UV irradiation and after exposure to inocula of a sewage treatment plant. The study reveals that most of the tested compounds and their PTPs were neither readily nor inherently biodegradable in the Organisation for Economic Co-operation and Development (OECD)-biodegradability tests. The study further demonstrates that PTPs are formed upon irradiation with an Hg lamp (UV light) and, to a lesser extent, upon irradiation with a Xe lamp (mimics sunlight). Comparing the nonirradiated with the corresponding irradiated solutions, a higher chronic toxicity against bacteria was found for the irradiated solutions of linezolid. Neither cytotoxicity nor genotoxicity was found in human cervical (HeLa) and liver (Hep-G2) cells for any of the investigated compounds or their PTPs. Antimicrobial activity of the tested fluoroquinolones was reduced after UV treatment, but it was not reduced after a 28-day exposure to inocula of a sewage treatment plant. This comparative study shows that PTPs can be formed as a result of UV treatment. The study further demonstrated that UV irradiation can be effective in reducing the antimicrobial activity of antibiotics, and consequently may help to reduce antimicrobial resistance in wastewaters. Nevertheless, the study also highlights that some PTPs may exhibit a higher ecotoxicity than the respective parent compounds. Consequently, UV treatment does not transform all micropollutants into harmless compounds and may not be a large-scale effluent treatment option.

http://www.ncbi.nlm.nih.gov/pubmed/26169816

FINDINGS

In the present study, in vitro toxicity as well as biopersistence and photopersistence of four artificial sweeteners, acesulfame, cyclamate, saccharine, and sucralose, and five antibiotics, levofloxacin, lincomycin, linezolid, marbofloxacin, and sarafloxacin, and of their phototransformation products or PTPs—their chemical breakdown elements when exposed to ultraviolet light from the sun—were investigated. The study reveals that most of the tested compounds and their phototransformation products were neither readily nor inherently biodegradable ... the study also highlights that some phototransformation products may exhibit a higher ecotoxicity than the respective parent compounds. Consequently, UV waste water treatment does not transform all micropollutants into harmless compounds and may not be a large-scale effluent treatment option for community treatment plants.

MANNITOL

Mannitol is a white, crystalline solid that looks and tastes sweet like sucrose. Medically it is used to treat increased intracranial pressure. It reduces pressure in the brain. It also has several industrial uses. In plants its purpose is to alleviate osmotic stress. Serious side effects may include worsening heart failure, electrolyte abnormalities, or low blood volume. It is unclear if it is safe in pregnancy. Mannitol is classified as a sugar alcohol; that is, it is derived from a sugar (mannose) by reduction. Other sugar alcohols include xylitol and sorbitol.

It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system. It was originally isolated from the flowering ash and called manna after its supposed resemblance to the Biblical food.

Medical Uses

Mannitol is used to reduce acutely raised intracranial pressure until more definitive treatment can be applied, e.g., after head trauma. It may also be used for certain cases of kidney failure with low urine output, decreasing pressure in the eye, to increase the elimination of certain toxins, ciguatera fish poisoning, and to treat fluid build up. Mannitol acts as an osmotic laxative in oral doses larger than 20 grams and is sometimes sold as a laxative for children. Mannitol is also commonly used in the circuit prime of a heart lung machine during cardiopulmonary bypass. The presence of mannitol preserves renal function during the times of low blood flow and pressure, while the patient is on bypass. The solution prevents the swelling of endothelial cells in the kidney, which may have otherwise reduced blood flow to this area and resulted in cell damage.

Mannitol can also be used to temporarily encapsulate a sharp object (such as a helix on a lead for an artificial pacemaker) while it is passed through the venous system. Because the mannitol dissolves readily in blood, the sharp point will become exposed at its destination. Mannitol is the primary ingredient of Mannitol Salt Agar, a bacterial growth medium, and is used in other laboratory growth mediums. Mannitol is also the first drug of choice for the treatment of acute glaucoma in veterinary medicine. It is administered as a 20% solution IV. It dehydrates the vitreous humor and, therefore, lowers the intraocular pressure.

Researchers from Tel Aviv University describe experiments that could lead to a new approach for treating Parkinson's disease using the common sweetener, mannitol. These findings were confirmed by a second study which measured the impact of mannitol on mice engineered to produce human α-synuclein, developed by Dr. Eliezer Masliah of the University of California, San Diego. After four months, the researchers found that the mice injected with mannitol also showed a dramatic reduction of α-synuclein in the brain possibly making it an effective Parkinson's Disease treatment. All chemicals added to our food are actually drugs and they were always drugs first.

Food Uses

Mannitol increases blood glucose to a lesser extent than sucrose (thus having a relatively low glycemic index) and is therefore used as a sweetener for people with diabetes, and in chewing gums. Although mannitol has a higher heat of solution than most sugar alcohols, its comparatively low solubility reduces the cooling effect usually found in mint candies and gums. However, when mannitol is completely dissolved in a product, it induces a strong cooling effect. It has a very low hygroscopicity – it does not pick up water from the air until the humidity level is 98%. This makes mannitol very useful as a coating for hard candies, dried fruits, and chewing gums, and it is often included as an ingredient in candies and chewing gum. The pleasant taste and mouthfeel of mannitol also makes it a popular excipient for chewable tablets. You'll find Mannitol in Pepto Bismol and many dozens if not hundreds of additional over-the-counter drugs, vitamins and sundries.

MANNITOL IN PEPTO BISMAL

Chewable Tablets

Each peppermint-flavoured chewable tablet contains bismuth subsalicylate 262 mg. Nonmedicinal ingredients: calcium carbonate, magnesium stearate, **mannitol, peppermint flavour, PVP, Red 27 Lake, sodium saccharin, and talc**.

Caplets

Each caplet contains bismuth subsalicylate 262 mg. Nonmedicinal ingredients: calcium carbonate, magnesium stearate, **mannitol, microcrystalline cellulose, polysorbate 80, PVP, Red 27 Lake, silica, and sodium carboxymethyl starch.**

Journal Of Neurosurgery • November 2015

Mannitol dosing error during inter-facility transfer for intracranial emergencies

Author information

Elliott CA1, MacKenzie M2, O'Kelly CJ1.

Abstract

OBJECT

Mannitol is commonly used to treat elevated intracranial pressure (ICP). The authors analyzed mannitol dosing errors at peripheral hospitals prior to or during transport to tertiary care facilities for intracranial emergencies. They also investigated the appropriateness of mannitol use based on the 2007 Brain Trauma Foundation guidelines for severe traumatic brain injury.

METHODS

The authors conducted a retrospective review of the Shock Trauma Air Rescue Society (STARS) electronic patient database of helicopter medical evacuations in Alberta, Canada, between 2004 and 2012, limited to patients receiving mannitol before transfer. They extracted data on mannitol administration and patient characteristics, including diagnosis, mechanism, Glasgow Coma Scale score, weight, age, and pupil status.

RESULTS

A total of 120 patients with an intracranial emergency received a mannitol infusion initiated at a peripheral hospital (median Glasgow Coma Scale score 6; range 3-13). Overall, there was a 22% dosing error rate, which comprised an underdosing rate (<0.25 g/kg) of 8.3% (10 of 120 patients), an overdosing rate (>1.5 g/kg) of 7.5% (9 of 120), and a non-bolus administration rate (>1 hour) of 6.7% (8 of 120). Overall, 72% of patients had a clear indication to receive mannitol as defined by meeting at least one of the following criteria based on Brain Trauma Foundation guidelines: neurological deterioration (11%), severe traumatic brain injury (69%), or pupillary abnormality (25%).

CONCLUSIONS

Mannitol administration at peripheral hospitals is prone to dosing error. Strategies such as a pretransport checklist may mitigate this risk.

http://www.ncbi.nlm.nih.gov/pubmed/26077141

“... several epidemiological studies have found that consumption of non-nutritive sweeteners (NNSs), mainly in diet sodas, is associated with increased risk to develop obesity, metabolic syndrome, and type 2 diabetes ... recent findings from our laboratory .. support the notion that non-nutritive sweeteners have [medically undesirable] metabolic effects.”

Physiology And Behavior • December 2015

Metabolic effects of non-nutritive sweeteners

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Abstract

Until recently, the general belief was that non-nutritive sweeteners (NNSs) were healthy sugar substitutes because they provide sweet taste without calories or glycemic effects. However, data from several epidemiological studies have found that consumption of NNSs, mainly in diet sodas, is associated with increased risk to develop obesity, metabolic syndrome, and type 2 diabetes. The main purpose of this article is to review recent scientific evidence supporting potential mechanisms that explain how “metabolically inactive” NNSs, which have few, if any, calories, might promote metabolic dysregulation. Three potential mechanisms, which are not mutually exclusive, are presented: 1) NNSs interfere with learned responses that contribute to control glucose and energy homeostasis, 2) NNSs interfere with gut microbiota and induce glucose intolerance, and 3) NNSs interact with sweet-taste receptors expressed throughout the digestive system that play a role in glucose absorption and trigger insulin secretion. In addition, recent findings from our laboratory showing an association between individual taste sensitivity to detect sucralose and sucralose’s acute effects on metabolic response to an oral glucose load are reported. Taken as a whole, data support the notion that NNSs have metabolic effects. More research is needed to elucidate the mechanisms by which NNSs may drive metabolic dysregulation and better understand potential effects of these commonly used food additives.

http://www.ncbi.nlm.nih.gov/pubmed/26095119

“Here we argue that Non Nutritive Sweeteners are not physiologically inert compounds and consider the potential biological mechanisms by which Non Nutritive Sweetener consumption may impact energy balance and metabolic function, including actions on oral and extra-oral sweet taste receptors, and effects on metabolic hormone secretion, cognitive processes (e.g. reward learning, memory, and taste perception), and gut microbiota.”

Physiology & Behavior • December 2015

Physiological mechanisms by which non-nutritive sweeteners may impact body weight and metabolism

Author information

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Abstract

Evidence linking sugar-sweetened beverage (SSB) consumption to weight gain and other negative health outcomes has prompted many individuals to resort to artificial, non-nutritive sweetener (NNS) substitutes as a means of reducing SSB intake. However, there is a great deal of controversy regarding the biological consequences of NNS use, with accumulating evidence suggesting that NNS consumption may influence feeding and metabolism via a variety of peripheral and central mechanisms. Here we argue that NNSs are not physiologically inert compounds and consider the potential biological mechanisms by which NNS consumption may impact energy balance and metabolic function, including actions on oral and extra-oral sweet taste receptors, and effects on metabolic hormone secretion, cognitive processes (e.g. reward learning, memory, and taste perception), and gut microbiota.

http://www.ncbi.nlm.nih.gov/pubmed/26048305

“These results indicate that aspartame induces apoptosis mainly via mitochondrial pathway involved in apoptosis due to oxygen toxicity.”

Environmental Toxicology And Pharmacology • January 2014

Aspartame-induced apoptosis in PC12 cells

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Abstract

Aspartame is an artificial sweetner added to many low-calorie foods. The safety of aspartame remains controversial even though there are many studies on its risks. In this study, to understand the physiological effects of trace amounts of artificial sweetners on cells, the effects of aspartame on apoptosis were investigated using a PC12 cell system. In addition, the mechanism of apoptosis induced by aspartame in PC12 cells and effects on apoptotic factors such as cytochrome c, apoptosis-inducing factor, and caspase family proteins were studied by Western blotting and RT-PCR. Aspartame-induced apoptosis in PC12 cells in a dose-dependent manner. In addition, aspartame exposure increased the expressions of caspases 8 and 9, and cytochrome c. These results indicate that aspartame induces apoptosis mainly via mitochondrial pathway involved in apoptosis due to oxygen toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/24355796

“Data suggest that cola drinking at early life stages may predispose to atherosclerosis progression later in life ...”

PLoS One • March 2014

Rate of atherosclerosis progression in ApoE-/- mice long after discontinuation of cola beverage drinking

Author information

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Abstract

This study was conducted in order to evaluate the effect of cola beverages drinking on atherosclerosis and test the hypothesis whether cola beverages consumption at early life stages might affect the development and progression of atherosclerosis later in life. ApoE-/- C57BL/6J mice (8 week-old) were randomized in 3 groups (n=20 each) according to free access to water (W), sucrose sweetened carbonated cola drink(C) or aspartame-acesulfame K sweetened carbonated ‘light’ cola drink (L) for the next 8 weeks. Drinking treatment was ended by switching C and L groups to drinking water. Four mice per group and time were sequentially euthanized: before treatment (8 weeks-old), at the end of treatment (16 weeks-old) and after treatment discontinuation (20 weeks-old, 24 weeks-old, 30 week-old mice). Aortic roots and livers were harvested, processed for histology and serial cross-sections were stained. Aortic plaque area was analyzed and plaque/media-ratio was calculated. Early consumption of cola drinks accelerated atherosclerotic plaque progression favoring the interaction between macrophages and myofibroblasts, without the participation of either T lymphocytes or proliferative activity. Plaque/media-ratio varied according to drink treatment ($F_{2,54}=3.433$, $p<0.04$) and mice age ($F_{4,54}=5.009$, $p<0.03$) and was higher in C and L groups compared with age-matched W group ($p<0.05$ at 16 weeks and 20 weeks, $p<0.01$ at 24 weeks and 30 weeks). Natural evolution of atherosclerosis in ApoE-/- mice (W group) evidenced atherosclerosis acceleration in parallel with a rapid increase in liver inflammation around the 20 weeks of age. Cola drinking within the 8-16 weeks of age accelerated atherosclerosis progression in ApoE-/- mice favoring aortic plaque enlargement (inward remodeling) over media thinning all over the study time. Data suggest that cola drinking at early life stages may predispose to atherosclerosis progression later in life in ApoE-/- mice.

Full Text with Graphs, Charts and 27 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3966732/

“Both MSG and ASM individually as well as in combination had significant disruptive effects on the cognitive responses, memory retention and learning capabilities of the mice in the order (MSG+ASM)>ASM>MSG. Furthermore, while MSG and ASM individually were unable to alter the brain neurotransmitters and the oxidative stress indices, their combination dose (MSG+ASM) decreased significantly the levels of neurotransmitters (dopamine and serotonin) and it also caused oxidative stress ...”

Neurotoxicology And Teratology • March 2014

Cognitive and biochemical effects of monosodium glutamate and aspartame, administered individually and in combination in male albino mice

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Abstract

The present study was designed to investigate the in vivo effects of monosodium glutamate (MSG) and aspartame (ASM) individually and in combination on the cognitive behavior and biochemical parameters like neurotransmitters and oxidative stress indices in the brain tissue of mice. Forty male Swiss albino mice were randomly divided into four groups of ten each and were exposed to MSG and ASM through drinking water for one month. Group I was the control and was given normal tap water. Groups II and III received MSG (8 mg/kg) and ASM (32 mg/kg) respectively dissolved in tap water. Group IV received MSG and ASM together in the same doses. After the exposure period, the animals were subjected to cognitive behavioral tests in a shuttle box and a water maze. Thereafter, the animals were sacrificed and the neurotransmitters and oxidative stress indices were estimated in their forebrain tissue. Both MSG and ASM individually as well as in combination had significant disruptive effects on the cognitive responses, memory retention and learning capabilities of the mice in the order (MSG+ASM)>ASM>MSG. Furthermore, while MSG and ASM individually were unable to alter the brain neurotransmitters and the oxidative stress indices, their combination dose (MSG+ASM) decreased significantly the levels of neurotransmitters (dopamine and serotonin) and it also caused oxidative stress by increasing the lipid peroxides measured in the form of thiobarbituric acid-reactive substances (TBARS) and decreasing the level of total glutathione (GSH). Further studies are required to evaluate the synergistic effects of MSG and ASM on the neurotransmitters and oxidative stress indices and their involvement in cognitive dysfunctions.

http://www.ncbi.nlm.nih.gov/pubmed/24556450

SYNERGY

Synergy is the interaction or cooperation of two or more organizations, substances, or other agents to produce a combined effect greater than the sum of their separate effects. For example, when aluminum and mercury molecules meet within the human body their negative neurological effects can be as much as 100 times greater than with either element alone.

THE DRUG PUSHERS

As you’ve read here, a combination of Monosodium Glutamate and Aspartame, found together in many processed foods, significantly decreases the levels of the neurotransmitters dopamine and serotonin. This is the same action that is expected to take place in the brain of prescription users when their medical professional prescribes SSRI inhibitors. Aspartame, Mannitol, Sucralose, Erythritol, High Fructose Corn Syrup, Acesulfame, Saccharin, Neotame, Lactitol, Xylitol and all of the artificial sweeteners are drugs and they have specific effects and unexpected effects just as all drugs do. Those effects can vary considerably and in severity from person to person. Corporate America is manufacturing and selling these drugs across the country and they’re drugs that make people seriously ill with deadly consequences. And they’re sold with total impunity. It’s a conspiracy of silence.

“Consumption of calorie-sweetened beverages has continued to increase and plays a role in the epidemic of obesity, the metabolic syndrome, and fatty liver disease.”

Diabetes Care • April 2014

Dietary sugar and body weight: Have we reached a crisis in the epidemic of obesity and diabetes?: Health be damned! Pour on the sugar

Author information

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Abstract

Sugar-sweetened drinks have been associated with several health problems. In the point narrative as presented below, we provide our opinion and review of the data to date that we need to reconsider consumption of dietary sugar based on the growing concern of obesity and type 2 diabetes. In the counterpoint narrative following our contribution, Drs. Kahn and Sievenpiper provide a defense and suggest that dietary sugar is not the culprit. Data from the National Health and Nutrition Examination Survey and U.S. Department of Agriculture dietary surveys along with commercial Homescan data on household purchases were used to understand changes in sugar and fructose consumption. Meta-analyses and randomized clinical trials were used to evaluate outcomes of beverage and fructose intake. About 75% of all foods and beverages contain added sugar in a large array of forms. Consumption of soft drinks has increased fivefold since 1950. Meta-analyses suggest that consumption of sugar-sweetened beverages (SSBs) is related to the risk of diabetes, the metabolic syndrome, and cardiovascular disease. Drinking two 16-ounce SSBs per day for 6 months induced features of the metabolic syndrome and fatty liver. Randomized controlled trials in children and adults lasting 6 months to 2 years have shown that lowering the intake of soft drinks reduced weight gain. Recent studies suggest a gene-SSB potential relationship. Consumption of calorie-sweetened beverages has continued to increase and plays a role in the epidemic of obesity, the metabolic syndrome, and fatty liver disease. Reducing intake of soft drinks is associated with less weight gain.

http://www.ncbi.nlm.nih.gov/pubmed/24652725

“These joint responses support our hypothesis and suggest that exposure to sucralose may induce neurological and oxidative mechanisms with potentially important consequences for animal behaviour and physiology.”

PLoS One • April 2014

Sucralose induces biochemical responses in Daphnia magna

Author information

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Abstract

The intense artificial sweetener sucralose has no bioconcentration properties, and no adverse acute toxic effects have been observed in standard ecotoxicity tests, suggesting negligible environmental risk. However, significant feeding and behavioural alterations have been reported in non-standard tests using aquatic crustaceans, indicating possible sublethal effects. We hypothesized that these effects are related to alterations in acetylcholinesterase (AChE) and oxidative status in the exposed animals and investigated changes in AChE and oxidative biomarkers (oxygen radical absorbing capacity, ORAC, and lipid peroxidation, TBARS) in the crustacean Daphnia magna exposed to sucralose (0.0001-5 mg L(-1)). The sucralose concentration was a significant positive predictor for ORAC, TBARS and AChE in the daphnids. Moreover, the AChE response was linked to both oxidative biomarkers, with positive and negative relationships for TBARS and ORAC, respectively. These joint responses support our hypothesis and suggest that exposure to sucralose may induce neurological and oxidative mechanisms with potentially important consequences for animal behaviour and physiology.

Full text, graph and 63 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3974716/

“Taken together, the studies performed by G.D. Searle in the 1970s and other chronic bioassays do not provide adequate scientific support for Aspartame safety. In contrast, recent results of life-span carcinogenicity bioassays on rats and mice published in peer-reviewed journals, and a prospective epidemiological study, provide consistent evidence of Aspartame’s carcinogenic potential.”

American Journal Of Industrial Medicine • April 2014

The carcinogenic effects of aspartame: The urgent need for regulatory re-evaluation

Author information

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Abstract

Aspartame (APM) is an artificial sweetener used since the 1980s, now present in >6,000 products, including over 500 pharmaceuticals. Since its discovery in 1965, and its first approval by the US Food and Drugs Administration (FDA) in 1981, the safety of APM, and in particular its carcinogenicity potential, has been controversial. The present commentary reviews the adequacy of the design and conduct of carcinogenicity bioassays on rodents submitted by G.D. Searle, in the 1970s, to the FDA for market approval. We also review how experimental and epidemiological data on the carcinogenic risks of APM, that became available in 2005 motivated the European Commission (EC) to call the European Food and Safety Authority (EFSA) for urgent re-examination of the available scientific documentation (including the Searle studies). The EC has further requested that, if the results of the evaluation should suggest carcinogenicity, major changes must be made to the current APM specific regulations. Taken together, the studies performed by G.D. Searle in the 1970s and other chronic bioassays do not provide adequate scientific support for APM safety. In contrast, recent results of life-span carcinogenicity bioassays on rats and mice published in peer-reviewed journals, and a prospective epidemiological study, provide consistent evidence of APM’s carcinogenic potential. On the basis of the evidence of the potential carcinogenic effects of APM herein reported, a re-evaluation of the current position of international regulatory agencies must be considered an urgent matter of public health.

http://www.ncbi.nlm.nih.gov/pubmed/24436139

“It is clear that long term aspartame exposure could alter the brain antioxidant status, and can induce apoptotic changes in [the] brain.”

Redox Biology • April 2014

Biochemical responses and mitochondrial mediated activation of apoptosis on long-term effect of aspartame in rat brain

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Abstract

Aspartame, an artificial sweetener, is very widely used in many foods and beverages. But there are controversies about its metabolite which is marked for its toxicity. Hence it is believed to be unsafe for human use. Previous studies have reported on methanol exposure with involvements of free radicals on excitotoxicity of neuronal apoptosis. Hence, this present study is proposed to investigate whether or not chronic aspartame (FDA approved Daily Acceptable Intake (ADI),40 mg/kg bwt) administration could release methanol, and whether or not it can induce changes in brain oxidative stress status and gene and protein expression of anti-apoptotic Bcl-2 and pro-apoptotic Bax and caspase-3 in the rat brain region. To mimic the human methanol metabolism, Methotrexate (MTX)-treated Wistar strain male albino rats were used and after the oral administration of aspartame, the effects were studied along with controls and MTX-treated controls. Aspartame exposure resulted with a significant increase in the enzymatic activity in protein carbonyl, lipid peroxidation levels, superoxide dismutase, glutathione-S-transferase, glutathione peroxidase and catalase activity in (aspartame MTX)-treated animals and with a significant decrease in reduced glutathione, glutathione reductase and protein thiol, pointing out the generation of free radicals. The gene and protein expression of pro apoptotic marker Bax showed a marked increase whereas the anti-apoptotic marker Bcl-2 decreased markedly indicating the aspartame is harmful at cellular level. It is clear that long term aspartame exposure could alter the brain antioxidant status, and can induce apoptotic changes in brain.

Full text, graphs, charts and 85 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085354/

“... pharmacological perturbations during perinatal growth can cause persistent effects on the function of white adipose tissue, altering susceptibility to obesity later in life. Accordingly, the current study established a developmental period in which saccharin at high concentrations reduces adiposity and increases lean and bone mass in male mice while decreasing generalized growth in female mice.”

Endocrinology • April 2014

Administration of saccharin to neonatal mice influences body composition of adult males and reduces body weight of females

Author information

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Abstract

Nutritional or pharmacological perturbations during perinatal growth can cause persistent effects on the function of white adipose tissue, altering susceptibility to obesity later in life. Previous studies have established that saccharin, a nonnutritive sweetener, inhibits lipolysis in mature adipocytes and stimulates adipogenesis. Thus, the current study tested whether neonatal exposure to saccharin via maternal lactation increased susceptibility of mice to diet-induced obesity. Saccharin decreased body weight of female mice beginning postnatal week 3. Decreased liver weights on week 14 corroborated this diminished body weight. Initially, saccharin also reduced male mouse body weight. By week 5, weights transiently rebounded above controls, and by week 14, male body weights did not differ. Body composition analysis revealed that saccharin increased lean and decreased fat mass of male mice, the latter due to decreased adipocyte size and epididymal, perirenal, and sc adipose weights. A mild improvement in glucose tolerance without a change in insulin sensitivity or secretion aligned with this leaner phenotype. Interestingly, microcomputed tomography analysis indicated that saccharin also increased cortical and trabecular bone mass of male mice and modified cortical bone alone in female mice. A modest increase in circulating testosterone may contribute to the leaner phenotype in male mice. Accordingly, the current study established a developmental period in which saccharin at high concentrations reduces adiposity and increases lean and bone mass in male mice while decreasing generalized growth in female mice.

Full text, graphs, charts and 92 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3959603/

“... artificial sweeteners are a newly recognized class of environmental contaminants due to their extreme persistence and ubiquitous occurrence in various aquatic ecosystems.”

Water Research • April 2014

Evaluating the environmental impact of artificial sweeteners: a study of their distributions, photodegradation and toxicities

Author information

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Abstract

While having a long tradition as safe food additives, artificial sweeteners are a newly recognized class of environmental contaminants due to their extreme persistence and ubiquitous occurrence in various aquatic ecosystems. Resistant to wastewater treatment processes, they are continuously introduced into the water environments. To date however, their environmental behavior, fate as well as long term ecotoxicological contributions in our water resources still remain largely unknown. As a first step in the comprehensive study of artificial sweeteners, this work elucidates the geographical/seasonal/hydrological interactions of acesulfame, cyclamate, saccharin and sucralose in an open coast system at an estuarine/marine junction. Higher occurrence of acesulfame (seasonal average: 0.22 µg L(-1)) and sucralose (0.05 µg L(-1)) was found in summer while saccharin (0.11 µg L(-1)) and cyclamate (0.10 µg L(-1)) were predominantly detected in winter. Seasonal observations of the four sweeteners suggest strong connections with the variable chemical resistance among different sweeteners. Our photodegradation investigation further projected the potential impact of persistent acesulfame and sucralose compounds under prolonged exposure to intensive solar irradiation. Real-time observation by UPLC-ESI/MS of the degradation profile in both sweeteners illustrated that formation of new photo by-products under prolonged UV irradiation is highly viable. Interestingly, two groups of kinetically behaved photodegradates were identified for acesulfame, one of which was at least six times more persistent than the parent compound. For the first time, acute toxicity for the degradates of both sweeteners were arbitrarily measured, revealing photo-enhancement factors of 575 and 17.1 for acesulfame and sucralose, respectively. Direct comparison of photodegradation results suggests that the phototoxicity of acesulfame degradation products may impact aquatic ecosystems. In an attempt to neutralize this prolonged environmental threat, the feasibility of UV/TiO2 as an effective mineralization process in wastewater treatment was evaluated for both sweeteners. Under an environmental and technical relevant condition, a >84% removal rate recorded within 30 min and complete photomineralization was achieved within 2 h and delivering the best cost efficiency comparing to existing removal methods. A compilation of distribution, degradation, toxicity and attenuation results presented in this paper will go through critical discussions to explore some current issues and to pinpoint solutions for a better control in the emergent contamination of artificial sweeteners.

http://www.ncbi.nlm.nih.gov/pubmed/24289948

“Cerebellar cortex is considered target areas of Aspartame neurotoxicity, while P. anisum oil [Anise Oil], when used in combination with Aspartame displays a protective action against neurotoxicity.”

Ultrastructural Pathology • May 2014

Ameliorative effect of Pimpinella anisum oil on immunohistochemical and ultrastuctural changes of cerebellum of albino rats induced by aspartame

Author information

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Abstract

The study aims to investigate the protective effect of Pimpinella anisum oil on aspartame (ASP) which resulted in cerebellar changes. The rats were divided into four equal groups: Group 1: (control group): served as control animals. Group 2: control P. anisum oil received .5 mL/kg/d/b wt. once daily. Group 3 (ASP group): received daily 250 mg/kg/b wt. of ASP dissolved in distilled water and given orally to the animals by intra-gastric tube for 2 months. Group 4: received .5 mL/kg/b wt. of prophylactic P. anisum oil once daily, followed by ASP after 2 h for 2 months. The histopathological approach revealed marked changes in the Purkinje cells, myleinated nerve fibers and granular cells of ASP-treated animals. Some of these cells appeared with deeply stained cytoplasm. Ultrastructural examination showed Purkinje cells with dilated rough endoplasmic reticulum and condensed mitochondria. Granular cells appeared with less c nuclei and surrounded by dissolution of most Mossy rosettes structures. Most myelinated nerve fibers showed thickening of myelinated sheath and others showed splitting of their myelin sheath. The histopathological, immunohistochemical and ultrastructural alterations were much less observed in concomitant use of P. anisum oil with ASP. Cerebellar cortex is considered target areas of ASP neurotoxicity, while P. anisum oil, when used in combination with ASP displays a protective action against neurotoxicity.

P. ANISUM OIL • ANISE

Anise, also called aniseed, is a flowering plant in the family Apiaceae native to the eastern Mediterranean region and Southwest Asia. Its flavor has similarities with some other spices, such as star anise, fennel, and licorice. Anise is sweet and very aromatic, distinguished by its characteristic flavor. The seeds, whole or ground, are used for preparation of tea (alone or in combination with other aromatic herbs), as well as in a wide variety of regional and ethnic confectioneries, including black jelly beans, British aniseed balls, Australian humbugs, New Zealand aniseed wheels, Italian pizzelle, German Pfeffernüsse and Springerle, Austrian Anisbögen, Dutch muisjes, New Mexican bizcochitos, and Peruvian picarones. It is a key ingredient in Mexican atole de anís and champurrado, which is similar to hot chocolate, and it is taken as a digestive after meals in India. The Ancient Romans often served spiced cakes with aniseed called mustaceoe at the end of feasts as a digestive aid. This tradition of serving cake at the end of festivities is the basis for the tradition of serving cake at weddings.

Anise is used to flavor Middle Eastern arak; Colombian aguardiente; French absinthe, anisette, and pastis; Greek ouzo; Bulgarian and Macedonian mastika; German Jägermeister; Swiss Appenzeller Alpenbitter; Italian sambuca; Dutch Brokmöpke; Portuguese, Peruvian, and Spanish anísado and Herbs de Majorca; Mexican Xtabentún; and Turkish rakı. These liquors are clear, but on addition of water become cloudy, a phenomenon known as the ouzo effect. It is believed to be one of the secret ingredients in the French liqueur Chartreuse. It is also used in some root beers, such as Virgil's in the United States.

The main use of anise in traditional European herbal medicine was for its carminative effect (reducing flatulence), as noted by John Gerard in his Great Herball, an early encyclopedia of herbal medicine: "*The seed wasteth and consumeth winde, and is good against belchings and upbraidings of the stomacke, alaieth gripings of the belly, provoketh urine gently, maketh abundance of milke, and stirreth up bodily lust: it staieth the laske (diarrhea), and also the white flux (leukorrhea) in women*." Anise has also been used to treat menstrual cramps and colic. The essential oil has reportedly been used as an insecticide against head lice and mites.

http://www.ncbi.nlm.nih.gov/pubmed/24684500

“Acesulfame K may increase Intestinal Fat Deposition in presence of insulin resistance.”

Chemico-biological Interactions • May 2014

Effects of three intense sweeteners on fat storage in the C. elegans model

Author information

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Abstract

Beverages sweetened with caloric sweeteners (CS), glucose, sucrose or high-fructose corn syrup, are associated with weight gain. Beverages sweetened with intense sweeteners (IS) are marketed as low-calorie substitutes to prevent beverages-associated weight gain. Using Caenorhabditis elegans, the effects on intestinal fat deposition (IFD) and pharyngeal pumping rate (PPR) of cola beverages sweetened with glucose, aspartame, or aspartame plus acesulfame-potassium (AceK) were compared. Control groups received Escherichia coli (OP50) only. Study I: the nematodes received additional glucose- or IS-sweetened beverages. Study II: the nematodes received additional glucose, aspartame, or aspartame plus AceK (AAK). Beverages containing CS or IS (aspartame or AAK) did not alter IFD in wild type (N2) or in daf-16 deficiency. The CS cola increased IFD in sir-2.1 deficiency ($P<0.05$). The AAK-cola increased IFD in daf-16/daf-2 deficiency and sir-2.1 deficiency ($P<0.05$). Glucose increased IFD in N2 and daf-16 deficiency ($P<0.05$). Aspartame showed a tendency towards reduced IFD in N2 and decreased IFD in daf-16/daf-2 deficiency ($P<0.05$). AAK increased IFD in daf-16 deficiency and sir-2.1 deficiency ($P<0.05$), and reversed the aspartame-induced reduction in IFD. The aspartame-sweetened cola increased the PPR in daf-16/daf-2 deficiency and daf-16 deficiency ($P<0.05$); similar results were obtained in N2 with both IS ($P<0.05$). AAK increased the PPR in daf-16/daf-2, daf-16, and sir-2.1 deficiencies ($P<0.05$). Thus, IS increased the PPR, a surrogate marker of lifespan. Aspartame may have an independent effect in reducing IFD to assist humans desiring weight loss. AceK may increase IFD in presence of insulin resistance.

http://www.ncbi.nlm.nih.gov/pubmed/24632416

“Saccharin consumption may have negative effects on sperm parameters, and increases the rate of sperm DNA fragmentation and apoptosis in mice.”

Iranian Journal Of Reproductive Medicine • May 2014

Saccharin consumption increases sperm DNA fragmentation and apoptosis in mice

Rahimipour M1, Talebi AR2, Anvari M2,
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Abstract

BACKGROUND

Saccharin is an artificial non-caloric sweetener that used to sweeten products such as drinks, candies, medicines, and toothpaste, but our bodies cannot metabolize it. Sodium saccharin is considered as an important factor in tumor promotion in male rats but not in humans.

OBJECTIVE

The objective of this study was to investigate the effect of saccharin consumption on sperm parameters and apoptosis in adult mice.

RESULTS

Following saccharin consumption, we had a reduction in sperm motility with respect to control animals (p=0.000). In addition, the sperm count diminished (17.70±1.11 in controls vs. 12.80±2.79 in case group, p=0.003) and the rate of sperm normal morphology decreased from 77.00±6.40 in control animals into 63.85±6.81 in saccharin-treated mice (p=0.001). Also, we saw a statistically significant increase in rates of sperm DNA damage and apoptosis in experimental group when compared to control one (p=0.001, p=0.002 respectively).

CONCLUSION

Saccharin consumption may have negative effects on sperm parameters, and increases the rate of sperm DNA fragmentation and apoptosis in mice.

http://www.ncbi.nlm.nih.gov/pubmed/25031574

“Aspartame is one of the most widely used artificial sweeteners globally. Data concerning acute neurotoxicity of aspartame is controversial, and knowledge on its chronic effect is limited. Aspartame treatment significantly alters the tyrosine hydroxylase activity and amino acids levels in the brain. Our data suggest that chronic use of aspartame may affect electrolyte homeostasis and monoamine neurotransmitter synthesis dose dependently, and this might have a possible effect on cognitive functions.”

International Journal Of Toxicology • May 2014

Chronic Effect of Aspartame on Ionic Homeostasis and Monoamine Neurotransmitters in the Rat Brain

Author information

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Abstract

Aspartame is one of the most widely used artificial sweeteners globally. Data concerning acute neurotoxicity of aspartame is controversial, and knowledge on its chronic effect is limited. In the current study, we investigated the chronic effects of aspartame on ionic homeostasis and regional monoamine neurotransmitter concentrations in the brain. Our results showed that aspartame at high dose caused a disturbance in ionic homeostasis and induced apoptosis in the brain. We also investigated the effects of aspartame on brain regional monoamine synthesis, and the results revealed that there was a significant decrease of dopamine in corpus striatum and cerebral cortex and of serotonin in corpus striatum. Moreover, aspartame treatment significantly alters the tyrosine hydroxylase activity and amino acids levels in the brain. Our data suggest that chronic use of aspartame may affect electrolyte homeostasis and monoamine neurotransmitter synthesis dose dependently, and this might have a possible effect on cognitive functions.

http://www.ncbi.nlm.nih.gov/pubmed/24872471

Nature • October 2014

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Author information

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Abstract

“Non-caloric artificial sweeteners” (NAS) are among the most widely used food additives worldwide, regularly consumed by lean and obese individuals alike. Non-caloric artificial sweetener consumption is considered safe and beneficial owing to their low caloric content, yet supporting scientific data remain sparse and controversial. Here we demonstrate that consumption of commonly used Non-caloric artificial sweetener formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota. These Non-caloric artificial sweetener-mediated deleterious metabolic effects are abrogated by antibiotic treatment, and are fully transferrable to germ-free mice upon faecal transplantation of microbiota configurations from Non-caloric artificial sweetener-consuming mice, or of microbiota anaerobically incubated in the presence of Non-caloric artificial sweeteners. We identify Non-caloric artificial sweetener-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrate similar Non-caloric artificial sweetener-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, our results link Non-caloric artificial sweetener consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive Non-caloric artificial sweetener usage.”

http://www.ncbi.nlm.nih.gov/pubmed/25231862

“Suez et al. (2014) recently demonstrated that artificial sweeteners alter gut microbial communities, leading to glucose intolerance in both mice and humans.”

Cell Metabolism • November 2014

A bitter aftertaste: unintended effects of artificial sweeteners on the gut microbiome

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Abstract

Intestinal microbial communities regulate a range of host physiological functions, from energy harvest and glucose homeostasis to immune development and regulation. Suez et al. (2014) recently demonstrated that artificial sweeteners alter gut microbial communities, leading to glucose intolerance in both mice and humans.

Full text, graphs, charts and 10 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494042/

“Results revealed that consuming non-caloric-sweetened beverages influences psychological processes in ways that - over time - may increase calorie intake ...”

Appetite • December 2014

The effect of non-caloric sweeteners on cognition, choice, and post-consumption satisfaction

Author information

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Abstract

Consumers often turn to non-caloric sweeteners (NCS) as a means of promoting a healthy body weight. However, several studies have now linked their long-term use to increased weight gain, raising the question of whether these products produce unintended psychological, physiological, or behavioral changes that have implications for weight management goals. In the following, we present the results of three experiments bearing on this issue, testing whether NCS-consumption influences how individuals think about and respond to food. Participants in each of our three experiments were randomly assigned to consume a sugar-sweetened beverage, an unsweetened beverage, or a beverage sweetened with NCS. We then measured their cognition (Experiment 1), product choice (Experiment 2), and subjective responses to a sugar-sweetened food (Experiment 3). Results revealed that consuming NCS-sweetened beverages influences psychological processes in ways that - over time - may increase calorie intake.

http://www.ncbi.nlm.nih.gov/pubmed/25128835

Journal Of Inorganic Biochemistry • December 2014

Combining anti-cancer drugs with artificial sweeteners: synthesis and anti-cancer activity of: saccharinate (sac) and thiosaccharinate (tsac) complexes cis-[Pt(sac)2(NH3)2] and cis-[Pt(tsac)2(NH3)2]

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Abstract

The new platinum(II) complexes cis-[Pt(sac)2(NH3)2] (sac=saccharinate) and cis-[Pt(tsac)2(NH3)2] (tsac=thiosaccharinate) have been prepared, the X-ray crystal structure of cis-[Pt(sac)2(NH3)2] x H2O reveals that both saccharinate anions are N-bound in a cis-arrangement being inequivalent in both the solid-state and in solution at room temperature. Preliminary anti-cancer activity has been assessed against A549 human alveolar type-II like cell lines with the thiosaccharinate complex showing good activity.

http://www.ncbi.nlm.nih.gov/pubmed/25216367

“These results suggest that consumption of artificially-sweetened soft drinks during pregnancy may play a role in offspring allergic disease development.”

PLoS One • February 2013

Consumption of artificially-sweetened soft drinks in pregnancy and risk of child asthma and allergic rhinitis

Author information

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Abstract

BACKGROUND

Past evidence has suggested a role of artificial sweeteners in allergic disease; yet, the evidence has been inconsistent and unclear.

OBJECTIVE

To examine relation of intake of artificially-sweetened beverages during pregnancy with child asthma and allergic rhinitis at 18 months and 7 years.

RESULTS

At 18 months, we found that mothers who consumed more artificially-sweetened non-carbonated soft drinks were 1.23 (95% CI: 1.13, 1.33) times more likely to report a child asthma diagnosis compared to non-consumers. Similar results were found for child wheeze. Consumers of artificially-sweetened carbonated drinks were more likely to have a child asthma diagnosis in the patient (1.30, 95% CI: 1.01, 1.66) and medication (1.13, 95% CI: 0.98, 1.29) registry, as well as self-reported allergic rhinitis (1.31, 95% CI: 0.98, 1.74) during the first 7 years of follow-up. We found no associations for sugar-sweetened soft drinks.

CONCLUSION

Carbonated artificially-sweetened soft drinks were associated with registry-based asthma and self-reported allergic rhinitis, while early childhood outcomes were related to non-carbonated soft drinks. These results suggest that consumption of artificially-sweetened soft drinks during pregnancy may play a role in offspring allergic disease development.

Full Text, Graphs, Charts and 46 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3584110/

“Fructose intake enhances lipogenesis and the production of uric acid. By worsening blood lipids, contributing to obesity, diabetes, fatty liver, and gout, fructose in the amounts currently consumed is hazardous to the health of some people.”

Advances In Nutrition • March 2013

Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people

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Abstract

Sugar intake in the United States has increased by >40 fold since the American Revolution. The health concerns that have been raised about the amounts of sugar that are in the current diet, primarily as beverages, are the subject of this review. Just less than 50% of the added sugars (sugar and high-fructose corn syrup) are found in soft drinks and fruit drinks. The intake of soft drinks has increased 5-fold between 1950 and 2000. Most meta-analyses have shown that the risk of obesity, diabetes, cardiovascular disease, and metabolic syndrome are related to consumption of beverages sweetened with sugar or high-fructose corn syrup. Calorically sweetened beverage intake has also been related to the risk of nonalcoholic fatty liver disease, and, in men, gout. Calorically sweetened beverages contribute to obesity through their caloric load, and the intake of beverages does not produce a corresponding reduction in the intake of other food, suggesting that beverage calories are “add-on” calories. The increase in plasma triglyceride concentrations by sugar-sweetened beverages can be attributed to fructose rather than glucose in sugar. Several randomized trials of sugar-containing soft drinks versus low-calorie or calorie-free beverages show that either sugar, 50% of which is fructose, or fructose alone increases triglycerides, body weight, visceral adipose tissue, muscle fat, and liver fat. Fructose is metabolized primarily in the liver. When it is taken up by the liver, ATP decreases rapidly as the phosphate is transferred to fructose in a form that makes it easy to convert to lipid precursors. Fructose intake enhances lipogenesis and the production of uric acid. By worsening blood lipids, contributing to obesity, diabetes, fatty liver, and gout, fructose in the amounts currently consumed is hazardous to the health of some people.

Full text, graphs, charts and 36 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3649102/

“These results suggest that the most negative consequences of consuming high-intensity sweeteners may occur in those most likely to use them for weight control, females consuming a “Westernized” diet and already prone to excess weight gain.”

Behavioral Neuroscience • April 2013

Adverse effects of high-intensity sweeteners on energy intake and weight control in male and obesity-prone female rats

Author information

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Abstract

The use of high-intensity sweeteners has been proposed as a method to combat increasing rates of overweight and obesity in the human population. However, previous work with male rats suggests that consumption of such sweeteners might contribute to, rather than ameliorate, weight gain. The goals of the present experiments were to assess whether intake of high-intensity sweeteners is associated with increased food intake and body weight gain in female rats; to evaluate whether this effect depends on composition of the maintenance diet (i.e., standard chow compared with diets high in energy, fat, and sugar [HE diets]); and to determine whether the phenotype of the rats with regard to propensity to gain weight on HE diets affects the consequences of consuming high-intensity sweeteners. The data demonstrated that female rats fed a low-fat, standard laboratory chow diet did not gain extra weight when fed yogurt dietary supplements sweetened with saccharin compared with those fed glucose-sweetened dietary supplements. However, female rats maintained on a “Westernized” diet high in fat and sugar (HE diet) showed significant increases in energy intake, weight gain, and adiposity when given saccharin-sweetened compared with glucose-sweetened yogurt supplements. These differences were most pronounced in female rats known to be prone to obesity prior to the introduction of the yogurt diets. Both selectively bred Crl:OP[CD] rats and outbred Sprague-Dawley rats fed an HE diet showing high levels of weight gain (diet-induced obese [DIO] rats) had increased weight gain in response to consuming saccharin-sweetened compared with glucose-sweetened supplements. However, in male rats fed an HE diet, saccharin-sweetened supplements produced extra weight gain regardless of obesity phenotype. These results suggest that the most negative consequences of consuming high-intensity sweeteners may occur in those most likely to use them for weight control, females consuming a “Westernized” diet and already prone to excess weight gain.

Full Text with Graphs, Charts and 74 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3985091/

Science Progress • April 2013

Averting comfortable lifestyle crises

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Abstract

How have climate change and diet shaped the evolution of human energy metabolism, and responses to vitamin C, fructose and uric acid? Through the last three millennia observant physicians have noted the association of inappropriate diets with increased incidence of obesity, heart disease, diabetes and cancer, and over the past 300 years doctors in the UK observed that overeating increased the incidence of these diseases. Anthropological studies of the Inuit culture in the mid-nineteenth century revealed that humans can survive and thrive in the virtual absence of dietary carbohydrate. In the 1960s, Cahill revealed the flexibility of human metabolism in response to partial and total starvation and demonstrated that type 2 diabetics were better adapted than healthy subjects to conserving protein during fasting. The potential role for brown adipose tissue thermogenesis in temperature maintenance and dietary calorie control was suggested by Rothwell and Stock from their experiments with 'cafeteria fed rats' in the 1980s. Recent advances in gene array studies and PET scanning support a role for this process in humans. The industrialisation of food processing in the twentieth century has led to increases in palatability and digestibility with a parallel loss of quality leading to overconsumption and the current obesity epidemic. The switch from animal to vegetable fats at the beginning of the twentieth century, followed by the rapid increase in sugar and fructose consumption from 1979 is mirrored by a steep increase in obesity in the 1980s, in the UK and USA. Containment of the obesity epidemic is compounded by the addictive properties of sugar which involve the same dopamine receptors in the pleasure centres of the brain as for cocaine, nicotine and alcohol. Of the many other toxic effects of excessive sugar consumption, immunocompromisation, kidney damage, atherosclerosis, oxidative stress and cancer are highlighted. The WHO and guidelines on sugar consumption include: alternative non-sugar sweeteners; toxic side-effects of aspartame. Stevia and xylitol as healthy sugar replacements; the role of food processing in dietary health; and beneficial effects of resistant starch in natural and processed foods. The rise of maize and soya-based vegetable oils have led to omega-6 fat overload and imbalance in the dietary ratio of omega-3 to omega-6 fats. This has led to toxicity studies with industrial trans fats; investigations on health risks associated with stress and comfort eating; and abdominal obesity. Other factors to consider are: diet, cholesterol and oxidative stress, as well as the new approaches to the chronology of eating and the health benefits of intermittent fasting.

http://www.ncbi.nlm.nih.gov/pubmed/24547668

Compendium • July 2013

Hidden dangers in the kitchen: common foods toxic to dogs and cats

Author information

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Abstract

Many foods and food additives that are safe for human consumption can be extremely toxic to pets. Recognizing the clinical signs and clinicopathologic changes associated with these toxins allows prompt initiation of appropriate therapy. As with many other toxins, decontamination and supportive care are the mainstays of therapy for food toxicosis. Educating owners about foods and food additives that are unsafe for dogs and cats can help prevent toxicosis.

http://www.ncbi.nlm.nih.gov/pubmed/23677840

“Our data suggest that chronic use of acesulfame K could affect cognitive functions, potentially via altering neuro-metabolic functions in male C57BL/6J mice.”

PLoS One • August 2013

Long-term artificial sweetener acesulfame potassium treatment alters neurometabolic functions in C57BL/6J mice

Author information

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Abstract

With the prevalence of obesity, artificial, non-nutritive sweeteners have been widely used as dietary supplements that provide sweet taste without excessive caloric load. In order to better understand the overall actions of artificial sweeteners, especially when they are chronically used, we investigated the peripheral and central nervous system effects of protracted exposure to a widely used artificial sweetener, acesulfame K (ACK). We found that extended ACK exposure (40 weeks) in normal C57BL/6J mice demonstrated a moderate and limited influence on metabolic homeostasis, including altering fasting insulin and leptin levels, pancreatic islet size and lipid levels, without affecting insulin sensitivity and bodyweight. Interestingly, impaired cognitive memory functions (evaluated by Morris Water Maze and Novel Objective Preference tests) were found in ACK-treated C57BL/6J mice, while no differences in motor function and anxiety levels were detected. The generation of an ACK-induced neurological phenotype was associated with metabolic dysregulation (glycolysis inhibition and functional ATP depletion) and neurosynaptic abnormalities (dysregulation of TrkB-mediated BDNF and Akt/Erk-mediated cell growth/survival pathway) in hippocampal neurons. Our data suggest that chronic use of ACK could affect cognitive functions, potentially via altering neuro-metabolic functions in male C57BL/6J mice.

Full Text, Graphs, Charts and 89 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3737213/

The C57BL/6 Mouse

C57BL/6, often referred to as “C57 Black 6”, “C57” or just “Black 6”, is a common inbred strain of laboratory mouse. The mouse has the most widely used “genetic background” for genetically modified mouse models of human disease due to availability of congenic strains, easy breeding and robustness. The C57BL/6 mouse was the second-ever mammalian species to have its entire genome published.

“Consumption of calorie-sweetened beverages and the fructose they contain has continued to increase and may play a role in the epidemic of obesity, the metabolic syndrome and fatty liver disease. Reducing intake of soft drinks is associated with less weight gain and metabolic improvement as well.”

Pediatric Obesity • August 2013

Calorie-sweetened beverages and fructose: what have we learned 10 years later

Author information

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Abstract

BACKGROUND
Sugar-sweetened drinks and the fructose they provide are associated with several health problems.
METHODS
Data from the Nielsen Homescan and product content were analysed for sweetener type using the Gladson Nutrition Database. Meta-analyses and randomized clinical trials were used to evaluate outcomes of beverage and fructose intake.
RESULTS
Over 70% of all foods contain some amounts of added sugar, and consumption of soft drinks has increased fivefold since 1950. Meta-analyses suggest that consumption of sugar-sweetened beverages is related to the risk of diabetes, the metabolic syndrome and cardiovascular disease in adults and in children. Drinking two sugar-sweetened beverages per day for 6 months induced features of the metabolic syndrome and fatty liver. Randomized, controlled trials in children and adults lasting from 6 months to 2 years have shown that lowering the intake of soft drinks reduced weight gain. Genetic factors influence the weight gain when drinking soft drinks.
CONCLUSION
Consumption of calorie-sweetened beverages and the fructose they contain has continued to increase and may play a role in the epidemic of obesity, the metabolic syndrome and fatty liver disease. Reducing intake of soft drinks is associated with less weight gain and metabolic improvement as well.

http://www.ncbi.nlm.nih.gov/pubmed/23625798

“This hypothesis suggested that both ulcerative colitis and Crohn’s disease are caused by weakening of the gut barrier due to damage of the protective mucus layer and the underlying tissue by the poorly inactivated digestive proteases resulting from a reduction of gut bacteria by dietary chemicals like saccharin and sucralose.”

World Journal Of Gastrointestinal Pathophysiology • August 2013

Why is damage limited to the mucosa in ulcerative colitis but transmural in Crohn’s disease?

Author information

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Abstract

It has been a big puzzle as why the inflammation of ulcerative colitis (UC) is limited to the mucosa, while in Crohn’s disease (CD) the inflammation is transmural and can be seen in all layers of the gut. Here, I give a tentative explanation extended from the unified hypothesis I proposed on the etiology of inflammatory bowel disease. This hypothesis suggested that both UC and CD are caused by weakening of the gut barrier due to damage of the protective mucus layer and the underlying tissue by the poorly inactivated digestive proteases resulting from a reduction of gut bacteria by dietary chemicals like saccharin and sucralose. However, the large amounts of bacteria in the colon make the recruitment of neutrophils and formation of crypt abscess the main manifestation of UC, while the infiltration of antigens and dietary particles in the small and large intestine mainly cause the recruitment of macrophages and formation of granulomas as the main manifestations in CD. The fast reacting and short life span of neutrophils make the fight and damage limited to the surface of the mucosa. In contrast, the long life span and constant movement of macrophages may bring the harmful agents deep into the tissue. Therefore, the pathogenesis of UC may be more like bacterial pneumonia, while CD may be more like pneumoconiosis or tuberculosis of the lung.

Full text with 7 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3740262/

“The results of this experiment indicate that long-term consumption of aspartame leads to an imbalance in the antioxidant/pro-oxidant status in the brain ...”

Drug And Chemical Toxicology • April 2013

Long-term consumption of aspartame and brain antioxidant defense status

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Abstract

The present study investigated the effect of long-term intake of aspartame, a widely used artificial sweetener, on antioxidant defense status in the rat brain. Male Wistar rats weighing 150-175 g were randomly divided into three groups as follows: The first group was given aspartame at a dose of 500 mg/kg body weight (b.w.); the second group was given aspartame at dose of 1,000 mg/kg b.w., respectively, in a total volume of 3 mL of water; and the control rats received 3 mL of distilled water. Oral intubations were done in the morning, daily for 180 days. The concentration of reduced glutathione (GSH) and the activity of glutathione reductase (GR) were significantly reduced in the brain of rats that had received the dose of 1,000 mg/kg b.w. of aspartame, whereas only a significant reduction in GSH concentration was observed in the 500-mg/kg b.w. aspartame-treated group. Histopathological examination revealed mild vascular congestion in the 1,000 mg/kg b.w. group of aspartame-treated rats. The results of this experiment indicate that long-term consumption of aspartame leads to an imbalance in the antioxidant/pro-oxidant status in the brain, mainly through the mechanism involving the glutathione-dependent system.

http://www.ncbi.nlm.nih.gov/pubmed/22385158

Water Research • September 2013

Occurrence of seven artificial sweeteners in the aquatic environment and precipitation of Tianjin, China

Author information

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Abstract

Seventy water samples, including wastewaters, tap waters, fresh surface waters, coastal waters, groundwaters, and precipitation samples, from Tianjin, China, were analyzed for seven commonly used artificial sweeteners (ASs). The concentrations of the investigated ASs were generally in the order of wastewater treatment plant (WWTP) influent > WWTP effluent > surface water > tap water > groundwater ≈ precipitation, while the composition profiles of ASs varied in different waters. Acesulfame, sucralose, cyclamate, and saccharin were consistently detected in surface waters and ranged from 50 ng/L to 0.12 mg/L, while acesulfame was the dominant AS in surface and tap waters. Aspartame was found in all of the surface waters at a concentration up to 0.21 μg/L, but was not found in groundwaters and tap waters. Neotame and neohesperidin dihydrochalcone were less frequently detected and the concentrations were low. The concentrations of the ASs in some of the surface waters were of the same order with those in the WWTP influents, but not with the effluents, indicating there are probably untreated discharges into the surface waters. The ASs were detected in precipitation samples with high frequency, and acesulfame, saccharin, and cyclamate were the predominant ASs, with concentrations ranging from 3.5 ng/L to 1.3 μg/L. A gross estimation revealed that precipitation may act as a source for saccharin and cyclamate in the surface environment of Tianjin city. Moreover, the presence of ASs in the atmosphere was primarily assessed by taking 4 air samples to evaluate their potential source in precipitation.

http://www.ncbi.nlm.nih.gov/pubmed/23866151

“Acesulfame, sucralose, cyclamate, and saccharin were consistently detected in surface waters and ranged from 50 ng/L to 0.12 mg/L, while acesulfame was the dominant artificial sweetener in surface and tap waters. Aspartame was found in all of the surface waters at a concentration up to 0.21 μg/L, but was not found in groundwaters and tap waters. Neotame and neohesperidin dihydrochalcone were less frequently detected and the concentrations were low. The concentrations of the artificial sweeteners in some of the surface waters were of the same order with those in the Waste Water Treatment Plants influents, but not with the effluents, indicating there are probably untreated discharges into the surface waters. The artificial sweeteners were detected in precipitation [rain] samples with high frequency, and acesulfame, saccharin, and cyclamate were the predominant artificial sweeteners, with concentrations ranging from 3.5 ng/L to 1.3 μg/L.”

“accumulating evidence suggests that frequent consumers of these sugar substitutes may also be at increased risk of excessive weight gain, metabolic syndrome, type 2 diabetes, and cardiovascular disease.”

Trends In Endocrinology And Metabolism • September 2013

Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements

Author information

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Abstract

The negative impact of consuming sugar-sweetened beverages on weight and other health outcomes has been increasingly recognized; therefore, many people have turned to high-intensity sweeteners like aspartame, sucralose, and saccharin as a way to reduce the risk of these consequences. However, accumulating evidence suggests that frequent consumers of these sugar substitutes may also be at increased risk of excessive weight gain, metabolic syndrome, type 2 diabetes, and cardiovascular disease. This paper discusses these findings and considers the hypothesis that consuming sweet-tasting but noncaloric or reduced-calorie food and beverages interferes with learned responses that normally contribute to glucose and energy homeostasis. Because of this interference, frequent consumption of high-intensity sweeteners may have the counterintuitive effect of inducing metabolic derangements.

Full Text with Graphs, Charts and 54 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3772345/

“... for infants and 95th percentile high-level consumers (especially those who choose sucralose containing foods), the estimated daily intakes of sucralose were very close to and higher than the acceptable daily intakes. Therefore, the sucralose concentration in sweetened beverages should be reduced; this would benefit the health of both high-level consumers and infants.”

International Journal Of Food Science & Nutrition • September 2013

Assessment of exposure of Korean consumers to acesulfame K and sucralose using a stepwise approach

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http://www.ncbi.nlm.nih.gov/pubmed/23631357

Abstract

Using a stepwise assessment of the exposure of Korean consumers to acesulfame K and sucralose, theoretical maximum daily intakes of the sweeteners were calculated using the Budget screening method, which resulted in values greater than the acceptable daily intakes (ADIs). Accordingly, the daily intakes of the sweeteners based on food consumption data and concentrations determined by instrumental analysis of 605 food samples were estimated for the more refined approach. The estimated daily intakes (EDIs) of all ordinary consumers were lower than the ADI, which was considered safe. However, for infants and 95th percentile high-level consumers (especially those who choose sucralose-containing foods), the EDIs of sucralose were very close to and higher than the ADI. Therefore, the sucralose concentration in sweetened beverages should be reduced; this would benefit the health of both high-level consumers and infants.

http://www.ncbi.nlm.nih.gov/pubmed/23631357

“In this context, obligatory ecotoxicity testing and stricter environmental regulations regarding food additives appear to be necessary.”

Environment International • October 2013

Ecotoxicity of artificial sweeteners and stevioside

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Abstract

Produced, consumed and globally released into the environment in considerable quantities, artificial sweeteners have been identified as emerging pollutants. Studies of environmental concentrations have confirmed the widespread distribution of acesulfame (ACE), cyclamate (CYC), saccharin (SAC) and sucralose (SUC) in the water cycle at levels that are among the highest known for anthropogenic trace pollutants. Their ecotoxicity, however, has yet to be investigated at a larger scale. The present study aimed to fill this knowledge gap by systematically assessing the influence of ACE, CYC and SAC and complementing the data on SUC. Therefore we examined their toxicity towards an activated sewage sludge community (30min) and applying tests with green algae Scenedesmus vacuolatus (24h), water fleas Daphnia magna (48h) and duckweed Lemna minor (7d). We also examined the effects caused by the natural sweetener stevioside. The high No Observed Effect Concentrations (NOECs) yielded by this initial evaluation indicated a low hazard and risk potential towards these aquatic organisms. For a complete risk assessment, however, several kinds of data are still lacking. In this context, obligatory ecotoxicity testing and stricter environmental regulations regarding food additives appear to be necessary.

http://www.ncbi.nlm.nih.gov/pubmed/24036324

“Sucralose and one of its hydrolysis products were found to be mutagenic at elevated concentrations in several testing methods. Cooking with sucralose at high temperatures was reported to generate chloropropanols, a potentially toxic class of compounds. Both human and rodent studies demonstrated that sucralose may alter glucose, insulin, and glucagon-like peptide 1 (GLP-1) levels. Taken together, these findings indicate that sucralose is not a biologically inert compound.”

The Journal Of Toxicology And Environmental Health Part B • Critical Reviews • December 2013

Sucralose, a synthetic organochlorine sweetener: overview of biological issues

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Abstract

Sucralose is a synthetic organochlorine sweetener (OC) that is a common ingredient in the world’s food supply. Sucralose interacts with chemosensors in the alimentary tract that play a role in sweet taste sensation and hormone secretion. In rats, sucralose ingestion was shown to increase the expression of the efflux transporter P-glycoprotein (P-gp) and two cytochrome P-450 (CYP) isozymes in the intestine. P-gp and CYP are key components of the presystemic detoxification system involved in first-pass drug metabolism. The effect of sucralose on first-pass drug metabolism in humans, however, has not yet been determined. In rats, sucralose alters the microbial composition in the gastrointestinal tract (GIT), with relatively greater reduction in beneficial bacteria. Although early studies asserted that sucralose passes through the GIT unchanged, subsequent analysis suggested that some of the ingested sweetener is metabolized in the GIT, as indicated by multiple peaks found in thin-layer radiochromatographic profiles of methanolic fecal extracts after oral sucralose administration. The identity and safety profile of these putative sucralose metabolites are not known at this time. Sucralose and one of its hydrolysis products were found to be mutagenic at elevated concentrations in several testing methods. Cooking with sucralose at high temperatures was reported to generate chloropropanols, a potentially toxic class of compounds. Both human and rodent studies demonstrated that sucralose may alter glucose, insulin, and glucagon-like peptide 1 (GLP-1) levels. Taken together, these findings indicate that sucralose is not a biologically inert compound.

With full text, graphs, charts and 374 incredible references, this is one great article!

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856475/

“Despite intense speculations about the carcinogenicity of aspartame, the latest studies show that its metabolite - diketopiperazine - is cancerogenic in the Central Nervous System. It contributes to the formation of tumors in the Central Nervous System such as gliomas, medulloblastomas and meningiomas.”

Folia Neuropathologia • December 2013

Effects of aspartame metabolites on astrocytes and neurons

Author information

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Abstract

Aspartame, a widespread sweetener used in many food products, is considered as a highly hazardous compound. Aspartame was discovered in 1965 and raises a lot of controversy up to date. Astrocytes are glial cells, the presence and functions of which are closely connected with the central nervous system (CNS). The aim of this article is to demonstrate the direct and indirect role of astrocytes participating in the harmful effects of aspartame metabolites on neurons. The artificial sweetener is broken down into phenylalanine (50%), aspartic acid (40%) and methanol (10%) during metabolism in the body. The excess of phenylalanine blocks the transport of important amino acids to the brain contributing to reduced levels of dopamine and serotonin. Astrocytes directly affect the transport of this amino acid and also indirectly by modulation of carriers in the endothelium. Aspartic acid at high concentrations is a toxin that causes hyperexcitability of neurons and is also a precursor of other excitatory amino acid - glutamates. Their excess in quantity and lack of astrocytic uptake induces excitotoxicity and leads to the degeneration of astrocytes and neurons. The methanol metabolites cause CNS depression, vision disorders and other symptoms leading ultimately to metabolic acidosis and coma. Astrocytes do not play a significant role in methanol poisoning due to a permanent consumption of large amounts of aspartame. Despite intense speculations about the carcinogenicity of aspartame, the latest studies show that its metabolite - diketopiperazine - is cancirogenic in the CNS. It contributes to the formation of tumors in the CNS such as gliomas, medulloblastomas and meningiomas. Glial cells are the main source of tumors, which can be caused inter alia by the sweetener in the brain. On the one hand the action of astrocytes during aspartame poisoning may be advantageous for neuroprotection while on the other it may intensify the destruction of neurons. The role of the glia in the pathogenesis of many CNS diseases is crucial.

http://www.ncbi.nlm.nih.gov/pubmed/23553132

International Journal Of Molecular Science • December 2013

Xylitol affects the intestinal microbiota and metabolism of daidzein in adult male mice

Author information

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Abstract

This study examined the effects of xylitol on mouse intestinal microbiota and urinary isoflavonoids. Xylitol is classified as a sugar alcohol and used as a food additive. The intestinal microbiota seems to play an important role in isoflavone metabolism. Xylitol feeding appears to affect the gut microbiota. We hypothesized that dietary xylitol changes intestinal microbiota and, therefore, the metabolism of isoflavonoids in mice. Male mice were randomly divided into two groups: those fed a 0.05% daidzein with 5% xylitol diet (XD group) and those fed a 0.05% daidzein-containing control diet (CD group) for 28 days. Plasma total cholesterol concentrations were significantly lower in the XD group than in the CD group ($p < 0.05$). Urinary amounts of equol were significantly higher in the XD group than in the CD group ($p < 0.05$). The fecal lipid contents (% dry weight) were significantly greater in the XD group than in the CD group ($p < 0.01$). The cecal microbiota differed between the two dietary groups. The occupation ratios of Bacteroides were significantly greater in the CD than in the XD group ($p < 0.05$). This study suggests that xylitol has the potential to affect the metabolism of daidzein by altering the metabolic activity of the intestinal microbiota and/or gut environment. Given that equol affects bone health, dietary xylitol plus isoflavonoids may exert a favorable effect on bone health.

Full text, graphs, charts and 48 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3876090/

DAIDZEIN

Daidzein can be found in food such as soybeans and soy products (and other foods) like tofu and textured vegetable protein. Soy isoflavones are a group of compounds found in and isolated from the soybean. Of note, total isoflavones in soybeans are—in general—37 percent daidzein, 57 percent genistein and 6 percent glycitein, according to USDA data. Soy germ contains 41.7 percent daidzein

BIOLOGICAL ACTIVITIES

Daidzein can be converted to its end metabolite S-equol in some humans based on the presence of certain intestinal bacteria. Based on several decades of research, S-equol has potential for significant health benefits. Daidzein has no classification in the United States, where it is not considered to be generally recognized as safe (GRAS), and has not been approved as a drug for any indication. It is a component of foods and dietary supplements derived from soy. Dietary supplements are not regulated as drugs in the U.S., and the labeling of dietary supplements in the U.S. may not describe the supplement as having any drug activity or effectiveness.

Scientists have studied some of the activities of daidzein in their laboratories, working with cells or with animals such as mice. Studies in cells and in animals sometimes give hints as to what a chemical might do when given to humans, but no one can know what a chemical does in humans until the chemical is tested in a clinical trial.

CELL PROLIFERATION STUDIES

Daidzein has both estrogenic and anti-estrogenic effects. Experiments in cells and in animals showed that lower concentrations stimulate breast tumor growth in in vitro and in vivo, and ihibits the antitumor effect of the cancer drug tamoxifen, but higher concentrations (above 10 μM) have the contrary effect. T47D:A18/PKC alpha tumor growth was demonstrated to be stimulated by genistein, but partially inhibited by daidzein; however, coadministration of tamoxifen with either daidzein or genistein produced tumors of greater size.

ANTIOXIDANT PROPERTIES

Scientific studies of daidzein's antioxidant properties have given contradictory results: some studies have shown antioxidant properties in laboratory experiments on cells, but in other experiments daidzein has caused oxidative stress on cells.

DAIDZEIN METABOLITE S-equol ACTIVITIES

Daidzein, when consumed from soy, is transformed in some humans, but not all, to produce S-equol [7-hydroxy-3-(49-hydroxyphenyl)-chroman]. Because it is a metabolite of daidzein, S-equol is not of plant origin. The molecular and physical structure of S-equol is similar to that of estradiol, the main sex hormone found in women. The ability to transform daidzein into S-equol is based on the presence of certain intestinal bacteria. In fact, several studies indicate that only 25 to 30 percent of the adult population of Western countries produces S-equol after eating soy foods containing isoflavones, significantly lower than the reported 50 to 60 percent frequency of equol-producers in adults from Japan, Korea, or China. Although still under investigation, the ability to produce S-equol may be associated with other health benefits, according to data from epidemiological and clinical trials. Studies in both animal models and humans have yielded data about the potential of S-equol use in menopause, breast and prostate cancer and bone health.

“Our results show that both physiology and locomotion behaviour were affected by exposure to sucralose. In Daphnia magna, the behavioural response was manifested as altered swimming height and increased swimming speed, whereas in gammarids the time to reach food and shelter was prolonged.”

Chemosphere • January 2012

Sucralose— an ecotoxicological challenger?

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Abstract

The non-calorie sweetener sucralose - sucrose containing three chlorine atoms - is intensively sweet and has become a popular substitute for sugar. Its widespread use, exceptional stability in combination with high water solubility have thus resulted in contamination of recipient waters. Earlier studies on sucralose in aquatic organisms indicate low bioaccumulation potential and negligible acute/chronic toxicity, but the close structural resemblance with sucrose in combination with the importance of sugar in nature, warrant a more detailed ecotoxicological assessment. The aim of this investigation was therefore to study behavioural and physiological effects of sucralose in crustaceans. Our results show that both physiology and locomotion behaviour were affected by exposure to sucralose. In Daphnia magna, the behavioural response was manifested as altered swimming height and increased swimming speed, whereas in gammarids the time to reach food and shelter was prolonged. Regardless if these behavioural responses were initiated via traditional toxic mechanisms or stimulatory effects, they should be considered as a warning, since exposed organisms may diverge from normal behaviour, which ultimately can have ecological consequences.

http://www.ncbi.nlm.nih.gov/pubmed/21955350

What Is electrolyte drink Pedialyte and why do we drink it?

It's a drink formulation that is supposed to restore mineral loss after vomiting and diarrhea. An electrolytic drink is especially helpful for little ones and the elderly, who are more susceptible to dehydration and mineral loss than the general population.

Pedialyte ingredients: Water, Dextrose. Less than 2% of the Following: Citric Acid, **Potassium Citrate, Sodium Chloride, Sodium Citrate, Sucralose, Acesulfame Potassium**, Zinc Gluconate, and **Artificial Flavor.**

In other words, Pedialyte is sugar water with minor amount of synthetic minerals added in, along with a generous dose of artificial colors and flavors.

Pedialyte Nutrition Facts

Electrolytes are minerals and nutrients found in the blood and other body fluids that carry an electric charge. So let's look at the mineral content of Pedialyte. See the chart at far right.

Now, let's take a look at coconut water.

When you open up a coconut, you have the meat, milk and water. The water is the highest in natural sugars and minerals, which are the most important to replenish after you've been sick. Interesting to note: coconut water's composition is very similar to human plasma. *So much so that, in wartime, coconut water has been used in blood transfusions! See the left chart of the two charts at right.
*(Source: Campbell-Falck, Darilyn et al. "The Intravenous Use of Coconut Water" American Journal of Emergency Medicine 18.1 (2000): 108-111.)

And it's loaded with nutrition.

As you can see, coconut water is very high in potassium (600 mg) when compared to its sodium content (200 mg). This is why we want to add high-quality sea or pink Himalayan salt to balance the mineral profile to be closer to a 1:1 ratio, so depending on your salt, 1/8-1/4 tsp. should do the trick. Any brand of coconut water, organic or not, with a little Pink Himalayan Salt or sea salt added for mineralization and you have a homemade product that's both cheaper and higher quality than Pedialyte, Pediasure and all of the competitors but what's far more important is that your electrolytic fluid is safe and has no chemicals in it. Easy and simple.

COCONUT WATER

Minerals	8 Ounces	
Amounts Per Selected Serving		%DV
Calcium	57.6 mg	6%
Iron	0.7 mg	4%
Magnesium	60.0 mg	15%
Phosphorus	48.0 mg	5%
Potassium	600 mg	17%
Sodium	252 mg	11%
Zinc	0.2 mg	2%
Copper	0.1 mg	5%
Manganese	0.3 mg	17%
Selenium	2.4 mcg	3%
Fluoride	~	

PEDIALYTE

Minerals	8 Ounces	
Amounts Per Selected Serving		%DV
Calcium	25.0 mg	2%
Iron	0.0 mg	0%
Magnesium	2.5 mg	1%
Phosphorus	25.0 mg	2%
Potassium	192 mg	5%
Sodium	253 mg	11%
Zinc	0.1 mg	0%
Copper	0.0 mg	1%
Manganese	~	~
Selenium	0.0 mcg	0%
Fluoride	~	

COST COMPARISON - JAN. 2016

The two largest bottles of Pedialyte pictured below, 1 liter bottles which are almost exactly 1 quart, average $13.97 each on Amazon.com. A comparable coconut water free of chemicals, Zico for example, runs $21.84 for a 12-pack of 14 ounce bottles. So Pedialyte gets you about 32 ounces for 14 bucks and Zico gets you 168 ounces for 22 dollars. This isn't rocket science is it?

“Consumption of sugar-sweetened beverages was associated with increased risk of Coronary Heart Disease and some adverse changes in lipids, inflammatory factors, and leptin.”

American Heart Association • April 2012

Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men

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Abstract

BACKGROUND

Sugar-sweetened beverage consumption is associated with weight gain and risk of type 2 diabetes mellitus. Few studies have tested for a relationship with coronary heart disease (CHD) or intermediate biomarkers. The role of artificially sweetened beverages is also unclear.

METHODS AND RESULTS

We performed an analysis of the Health Professionals Follow-Up Study, a prospective cohort study including 42 883 men. Associations of cumulatively averaged sugar-sweetened (eg, sodas) and artificially sweetened (eg, diet sodas) beverage intake with incident fatal and nonfatal CHD (myocardial infarction) were examined with proportional hazard models. There were 3683 CHD cases over 22 years of follow-up. Participants in the top quartile of sugar-sweetened beverage intake had a 20% higher relative risk of CHD than those in the bottom quartile (relative risk=1.20; 95% confidence interval, 1.09-1.33; P for trend <0.01) after adjustment for age, smoking, physical activity, alcohol, multivitamins, family history, diet quality, energy intake, body mass index, pre-enrollment weight change, and dieting. Artificially sweetened beverage consumption was not significantly associated with CHD (multivariate relative risk=1.02; 95% confidence interval, 0.93-1.12; P for trend=0.28). Adjustment for self-reported high cholesterol, high triglycerides, high blood pressure, and diagnosed type 2 diabetes mellitus slightly attenuated these associations. Intake of sugar-sweetened but not artificially sweetened beverages was significantly associated with increased plasma triglycerides, C-reactive protein, interleukin-6, and tumor necrosis factor receptors 1 and 2 and decreased high-density lipoprotein, lipoprotein(a), and leptin (P<0.02).

CONCLUSIONS

Consumption of sugar-sweetened beverages was associated with increased risk of CHD and some adverse changes in lipids, inflammatory factors, and leptin. Artificially sweetened beverage intake was not associated with CHD risk or biomarkers.

Full Text, Graphs, Charts and 38 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3368965/

“This paper aims to provide a detailed description of a unified hypothesis regarding the etiology of Inflammatory Bowel Disease, including the cause [Sucralose] and mechanism of Inflammatory Bowel Disease, as well as the relationship between Ulcerative Colitis and Crohn’s Disease.”

World Journal Of Gastroenterology • April 2012

Etiology of inflammatory bowel disease: a unified hypothesis

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Abstract

Inflammatory bowel disease (IBD), including both ulcerative colitis (UC) and Crohn’s disease (CD), emerged and dramatically increased for about a century. Despite extensive research, its cause remains regarded as unknown. About a decade ago, a series of findings made me suspect that saccharin may be a key causative factor for IBD, through its inhibition on gut bacteria and the resultant impaired inactivation of digestive proteases and over digestion of the mucus layer and gut barrier (the Bacteria-Protease-Mucus-Barrier hypothesis). It explained many puzzles in IBD such as its emergence and temporal changes in last century. Recently I further found evidence suggesting sucralose may be also linked to IBD through a similar mechanism as saccharin and have contributed to the recent worldwide increase of IBD. This new hypothesis suggests that UC and CD are just two symptoms of the same morbidity, rather than two different diseases. They are both caused by a weakening in gut barrier and only differ in that UC is mainly due to increased infiltration of gut bacteria and the resultant recruitment of neutrophils and formation of crypt abscess, while CD is mainly due to increased infiltration of antigens and particles from gut lumen and the resultant recruitment of macrophages and formation of granulomas. It explained the delayed appearance but accelerated increase of CD over UC and many other phenomena. This paper aims to provide a detailed description of a unified hypothesis regarding the etiology of IBD, including the cause and mechanism of IBD, as well as the relationship between UC and CD.

Full text, graphs, charts and 171 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3332284/

“A metabolic profile indicating increased risk of diabetes mellitus and cardiovascular disease was observed in animals given access to sugar-sweetened beverages. Notably, ‘free’ fructose disrupted glucose homeostasis more than did ‘bound’ fructose, thus posing a greater risk of progression to type 2 diabetes.”

European Journal Of Nutrition • June 2012

Metabolic and behavioural effects of sucrose and fructose/glucose drinks in the rat

Author information

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Abstract

PURPOSE

Overconsumption of sugar-sweetened beverages, in particular carbonated soft drinks, promotes the development of overweight and obesity and is associated with metabolic disturbances, including intrahepatic fat accumulation and metabolic syndrome. One theory proposes that drinks sweetened with high-fructose corn syrup are particularly detrimental to health, as they contain fructose in its ‘free’ monosaccharide form. This experiment tested whether consuming ‘free’ fructose had a greater impact on body weight and metabolic abnormalities than when consumed ‘bound’ within the disaccharide sucrose.

METHODS

Male Hooded Wistar rats were given free access for 56 days to 10% sucrose (Group Suc), 10%, 50/50 fructose/glucose (Group FrucGluc) or water control drinks (Group Control), plus chow. Caloric intake and body weights were measured throughout the protocol, and the following metabolic indices were determined between days 54 and 56: serum triglycerides, liver triglycerides, retroperitoneal fat and oral glucose tolerance.

RESULTS

Animals with access to sugar beverages consumed 20% more calories, but did not show greater weight gain than controls. Nevertheless, they developed larger abdominal fat pads, higher triglyceride levels and exhibited impaired insulin/glucose homeostasis. Comparison of the two sugars revealed increased fasting glycaemia in the FrucGluc group, but not in Suc group, whereas the Suc group was more active in an open field.

CONCLUSIONS

A metabolic profile indicating increased risk of diabetes mellitus and cardiovascular disease was observed in animals given access to sugar-sweetened beverages. Notably, ‘free’ fructose disrupted glucose homeostasis more than did ‘bound’ fructose, thus posing a greater risk of progression to type 2 diabetes.

http://www.ncbi.nlm.nih.gov/pubmed/21800086

“Although the concentrations of Acesulfame K and Sucralose are among the highest measured for anthropogenic trace pollutants found in surface water, groundwater, and drinking water, the levels are at least three orders of magnitude lower than organoleptic threshold values. However, eco-toxicology studies are scarce and have focused on Sucralose. Thus, further research is needed both on identification of transformation products and on the eco-toxicological impact of artificial sweeteners and their transformation products.”

Analytical And Bioanalytical Chemistry • July 2012

Artificial sweeteners—a recently recognized class of emerging environmental contaminants: a review

Author information

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Abstract

An overview is given of existing trace analytical methods for the determination of seven popular artificial sweeteners [acesulfame (ACE), aspartame, cyclamate (CYC), neotame, neohesperidine dihydrochalcone, saccharin (SAC), and sucralose (SUC)] from aqueous environmental samples. Liquid chromatography-electrospray ionization tandem mass spectrometry and liquid chromatography-electrospray ionization high-resolution mass spectrometry are the methods most widely applied, either directly or after solid-phase extraction. Limits of detection and limits of quantification down to the low nanogram per liter range can be achieved. ACE, CYC, SAC, and SUC were detected in wastewater treatment plants in high microgram per liter concentrations. Per capita loads of individual sweeteners can vary within a wide range depending on their use in different countries. Whereas CYC and SAC are usually degraded by more than 90% during wastewater treatment, ACE and SUC pass through wastewater treatment plants mainly unchanged. This suggests their use as virtually perfect markers for the study of the impact of wastewater on source waters and drinking waters. In finished water of drinking water treatment plants using surface-water-influenced source water, ACE and SUC were detected in concentrations up to 7 and 2.4 µg/L, respectively. ACE was identified as a precursor of oxidation byproducts during ozonation, resulting in an aldehyde intermediate and acetic acid. Although the concentrations of ACE and SUC are among the highest measured for anthropogenic trace pollutants found in surface water, groundwater, and drinking water, the levels are at least three orders of magnitude lower than organoleptic threshold values. However, ecotoxicology studies are scarce and have focused on SUC. Thus, further research is needed both on identification of transformation products and on the ecotoxicological impact of artificial sweeteners and their transformation products.

http://www.ncbi.nlm.nih.gov/pubmed/22543693

Obesity Reviews • August 2013

Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases

Author information

By F.B. Hu

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Abstract

Sugar-sweetened beverages (SSBs) are the single largest source of added sugar and the top source of energy intake in the U.S. diet. In this review, we evaluate whether there is sufficient scientific evidence that decreasing SSB consumption will reduce the prevalence of obesity and its related diseases. Because prospective cohort studies address dietary determinants of long-term weight gain and chronic diseases, whereas randomized clinical trials (RCTs) typically evaluate short-term effects of specific interventions on weight change, both types of evidence are critical in evaluating causality. Findings from well-powered prospective cohorts have consistently shown a significant association, established temporality and demonstrated a direct dose-response relationship between SSB consumption and long-term weight gain and risk of type 2 diabetes (T2D). A recently published meta-analysis of RCTs commissioned by the World Health Organization found that decreased intake of added sugars significantly reduced body weight (0.80 kg, 95% confidence interval [CI] 0.39-1.21; $P<0.001$), whereas increased sugar intake led to a comparable weight increase (0.75 kg, 0.30-1.19; $P=0.001$). A parallel meta-analysis of cohort studies also found that higher intake of SSBs among children was associated with 55% (95% CI 32-82%) higher risk of being overweight or obese compared with those with lower intake. Another meta-analysis of eight prospective cohort studies found that one to two servings per day of SSB intake was associated with a 26% (95% CI 12-41%) greater risk of developing T2D compared with occasional intake (less than one serving per month). Recently, two large RCTs with a high degree of compliance provided convincing data that reducing consumption of SSBs significantly decreases weight gain and adiposity in children and adolescents. Taken together, the evidence that decreasing SSBs will decrease the risk of obesity and related diseases such as T2D is compelling. Several additional issues warrant further discussion. First, prevention of long-term weight gain through dietary changes such as limiting consumption of SSBs is more important than short-term weight loss in reducing the prevalence of obesity in the population. This is due to the fact that once an individual becomes obese, it is difficult to lose weight and keep it off. Second, we should consider the totality of evidence rather than selective pieces of evidence (e.g. from short-term RCTs only). Finally, while recognizing that the evidence of harm on health against SSBs is strong, we should avoid the trap of waiting for absolute proof before allowing public health action to be taken.

http://www.ncbi.nlm.nih.gov/pubmed/23763695

Diet Sodas Polluting Grand River With Artificial Sweeteners

Good news! You no longer have to sweeten your coffee or tea to get the flavour you're looking for. Just use the water from the Grand River to make your beverage. Apparently it is so polluted with artificial sweeteners that scientists can use this fact to follow the movement of treated waste in the region's water supply.

The artificial sweeteners found were cyclamate (banned in North America), saccharin, sucralose (Splenda), and acesulfame (known as Acesulfame-K or Acesulfame Potassium). They all provide no calories, mainly because they are not broken down by the human digestive system. What is startling about this study is that the amounts found in the river were much higher than what has been found in other water systems in other parts of the world.

Twenty-three sites along the Grand River were part of the study conducted jointly by Environment Canada and the University of Waterloo. At one site, researchers calculated that the consumption would have to be 90,000 to 190,000 cans of diet soda a day to account for the amount of acesulfame they found. The surrounding area is home to about 1,000,000 people. The purpose of the study was to see if chemicals could be used to trace when human waste enters into the water system, both from treatment plants and from septic tanks where waste may be seeping into groundwater.

Now, you did read that correctly. They were not looking to see, or concerned with, how much we are polluting the water with all the artificial crap that is in our food and elsewhere. No, they were looking for chemicals that could be used to track human waste. Who knew pollution could have such a purpose. I suppose that's just a sign of the times where chemicals in the water are so normal that scientists see them as helpers for determining other issues.

However, researchers did point out that the long term effects to both human and aquatic life are "unknown". This should at least be alarming to all of us as "unknown" health effects never turn out to be a good thing. So remember this information the next time someone makes fun of you for drinking bottled water or filtered water (hopefully re-mineralized). And think twice before using tap water for cooking or making tea and coffee.

More importantly, if you are someone who actually thinks diet soda is going to help you lose weight or prevent weight gain, then perhaps you need to really take a hard look at your thought processes. Your body needs nutrients and that includes those found in natural sweeteners. Pure honey, pure maple syrup, sucanat, coconut sweetener and palm sugar are all nutrient–dense and low glycemic. Providing the body with sufficient nutrients will provide steady energy, stable blood sugar, and prevent cravings which will do a lot more for proper weight management than any artificial sweetener could ever do.

Source:

Artificial Sweeteners in a Large Canadian River Reflect Human Consumption in the Watershed, John Spoelstra, Sherry L. Schiff, Susan J. Brown, Published: December 11, 2013, PLOS One, DOI: 10.1371/journal.pone.0082706 (see next page).

PLoSOne • December 2013

Artificial Sweeteners in a Large Canadian River Reflect Human Consumption in the Watershed

Author information
By John Spoelstra, Sherry L. Schiff and Susan J. Brown, John Spoelstra, Susan J. Brown
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Abstract

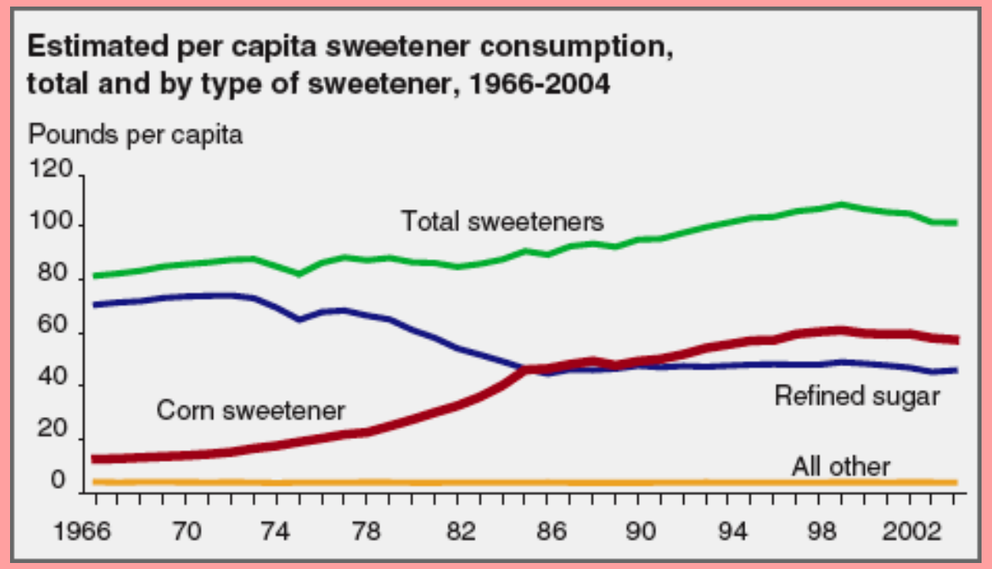
Artificial sweeteners have been widely incorporated in human food products for aid in weight loss regimes, dental health protection and dietary control of diabetes. Some of these widely used compounds can pass non-degraded through wastewater treatment systems and are subsequently discharged to groundwater and surface waters. Measurements of artificial sweeteners in rivers used for drinking water production are scarce. In order to determine the riverine concentrations of artificial sweeteners and their usefulness as a tracer of wastewater at the scale of an entire watershed, we analyzed samples from 23 sites along the entire length of the Grand River, a large river in Southern Ontario, Canada, that is impacted by agricultural activities and urban centres. Municipal water from household taps was also sampled from several cities within the Grand River Watershed. Cyclamate, saccharin, sucralose, and acesulfame were found in elevated concentrations despite high rates of biological activity, large daily cycles in dissolved oxygen and shallow river depth. The maximum concentrations that we measured for sucralose (21 µg/L), cyclamate (0.88 µg/L), and saccharin (7.2 µg/L) are the highest reported concentrations of these compounds in surface waters to date anywhere in the world. Acesulfame persists at concentrations that are up to several orders of magnitude above the detection limit over a distance of 300 km and it behaves conservatively in the river, recording the wastewater contribution from the cumulative population in the basin. Acesulfame is a reliable wastewater effluent tracer in rivers. Furthermore, it can be used to assess rates of nutrient assimilation, track wastewater plume dilution, separate human and animal waste contributions and determine the relative persistence of emerging contaminants in impacted watersheds where multiple sources confound the usefulness of other tracers. The effects of artificial sweeteners on aquatic biota in rivers and in the downstream Great Lakes are largely unknown.

PLOS ONE Staff • August 2014

Correction:
Artificial Sweeteners in a Large Canadian River Reflect Human Consumption in the Watershed

The maximum value for the concentration of cyclamate appears incorrectly throughout the paper as 0.88 µg/L. The correct maximum value for the concentration of cyclamate is 2.4 µg/L. This error appears in the Abstract, the first and second paragraph of the Results and Discussion and the last row of Table 1. **Cyclamate was almost 2.8 (2.7727) times higher than originally reported.**

Source:
http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0082706



Chemical Senses • October 2012

Rationale for further medical and health research on high-potency sweeteners

By S.S. Schiffman
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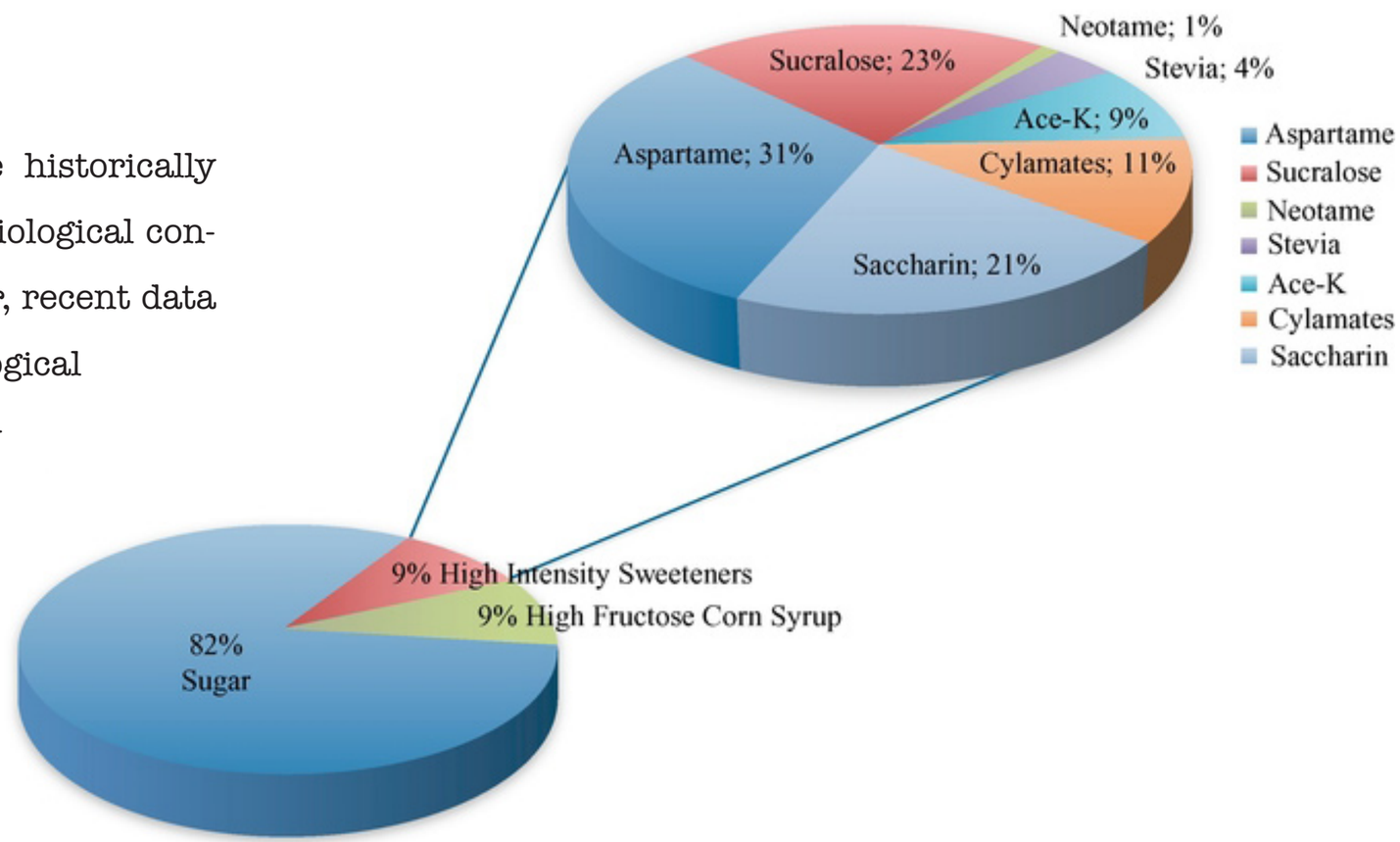
Abstract

"High-potency or artificial sweeteners have historically been considered inert compounds without physiological consequences other than taste sensations. However, recent data suggest that some of these sweeteners have biological effects that may impact human health. Furthermore, there are significant gaps in our current knowledge of the pharmacokinetics of these sweeteners, their potential for "sweetener-drug interactions" and their impact on appetite and body weight regulation. Nine research needs are described that address some of the major unknown issues associated with ingestion of high-potency sweeteners."

THE GLOBAL HIGH INTENSITY SWEETENER MARKET



Full text, graphs, charts and 86 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3440882/

“In conclusion, the consumption of aspartame leads to histopathological lesions in the liver and alterations of the genetic system in the liver and bone marrow of mother albino rats and their offspring. These toxicological changes were directly proportional to the duration of its administration and improved after its withdrawal.”

Pakistan Journal Of Biological Sciences • October 2012

Cytotoxic effect of aspartame (diet sweet) on the histological and genetic structures of female albino rats and their offspring

Author information

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Abstract

The present study evaluated the effect of aspartame intake on the histological and genetic structures of mother albino rats and their offspring. Sixty adult female albino rats and 180 of their offspring were equally divided into two groups (control and treated), each group divided into three subgroups. Each subgroup consisted of 10 pregnant rats and 30 of their offspring. The experimental design divided into three periods: (1) the gestation period (subgroup one), (2) the gestation period and three weeks after delivery (subgroup two) and (3) animals in the third subgroup treated as subgroup two then left till the end of the ninth week after delivery. Each pregnant rat in the treated subgroups was given a single daily dose of 1 mL aspartame solution (50.4 mg) by gastric gavage throughout the time intervals of experimental design. At the end of each experimental period for control and treated subgroups, the liver of half of both control and treated groups were subjected for histological study while the liver and bone marrow of the other halves were subjected for cytogenetic studies. Body weight of both groups were recorded individually twice weekly in the morning before offering the diet. The results revealed that the rats and their offspring in the subgroups of control animals showed increases in body weight, normal histological sections, low chromosomal aberration and low DNA fragmentation. The treated animals in the three subgroups rats and their offspring revealed decreases in body weight, high histological lesions, increases in the chromosomal aberration and DNA fragmentation compared with control groups. In conclusion, the consumption of aspartame leads to histopathological lesions in the liver and alterations of the genetic system in the liver and bone marrow of mother albino rats and their offspring. These toxicological changes were directly proportional to the duration of its administration and improved after its withdrawal.

http://www.ncbi.nlm.nih.gov/pubmed/24159687

“These findings suggest impaired memory performance and increased brain oxidative stress by repeated aspartame administration.”

European Review For Medical And Pharmacological Sciences • December 2012

Studies on the effects of aspartame on memory and oxidative stress in brain of mice

Author information

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Abstract

OBJECTIVE

The dipeptide aspartame (N-L-alpha-aspartyl-Lphenylalanine, 1-methyl ester; alpha-APM) is one of the most widely used artificial sweeteners. The present study aimed to investigate the effect of repeated administration of aspartame in the working memory version of Morris water maze test, on oxidative stress and brain monoamines in brain of mice.

MATERIALS AND METHODS

Aspartame (0.625, 1.875 or 5.625 mg/kg) was administered once daily subcutaneously for 2 weeks and mice were examined four times a week for their ability to locate a submerged plate. Malondialdehyde (MDA), reduced glutathione (GSH), nitric oxide levels (the concentrations of nitrite/nitrate) and glucose were determined in brain.

RESULTS

Only at the highest dose of 5.625 mg/kg, did aspartame significantly impaired water maze performance. The mean time taken to find the escape platform (latency) over 2 weeks was significantly delayed by aspartame 5.625 mg/kg, compared with the saline-treated control group. Significant differences occurred only on the first trial to find the escape platform. Significant increase in brain MDA by 16.5% and nitric oxide by 16.2% and a decrease in GSH by 25.1% and glucose by 22.5% occurred after treatment with aspartame at 1.875 mg/kg. Aspartame administered at 5.625 mg/kg significantly increased brain MDA by 43.8%, nitric oxide by 18.6% and decreased GSH by 32.7% and glucose by 25.8%. Aspartame caused dose-dependent inhibition of brain serotonin, noradrenaline and dopamine.

CONCLUSIONS

These findings suggest impaired memory performance and increased brain oxidative stress by repeated aspartame administration. The impaired memory performance is likely to involve increased oxidative stress as well as decreased brain glucose availability.

http://www.ncbi.nlm.nih.gov/pubmed/23280025

“Several 10-week to 26-week randomized trials of sugar-containing soft drinks show increases in triglycerides, body weight, and visceral adipose tissue; there were also increases in muscle fat and liver fat, which might lead to non-alcoholic-fatty liver disease.”

Current Atherosclerosis Reports • December 2012

Fructose and risk of cardiometabolic disease

By GA Bray

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Abstract

Fructose and glucose in soft drinks and fruit drinks account for just under 50 % of added sugars. Soft drinks intake has risen five-fold between 1950 and 2000, and this increase in intake of simple sugars has raised health concerns. The risks of cardiovascular disease, obesity and the metabolic syndrome have all been related to consumption of sugar-sweetened beverages in several, but not all meta-analyses. Fructose and sugar-sweetened beverages have also been related to the risk of gout in men, and to non-alcoholic fatty liver disease. Studies show that the calories in sugar-sweetened beverages do not produce an adequate reduction in the intake of other foods, leading to increased caloric intake. Plasma triglycerides are increased by sugar-sweetened beverages, and this increase appears to be due to fructose, rather than to glucose in sugar. Several 10-week to 26-week randomized trials of sugar-containing soft drinks show increases in triglycerides, body weight, and visceral adipose tissue; there were also increases in muscle fat and liver fat, which might lead to non-alcoholic-fatty liver disease.

http://www.ncbi.nlm.nih.gov/pubmed/22949106

Human And Experimental Toxicology • February 2011

Effect of saccharin on albino rats' blood indices and the therapeutic action of vitamins C and E

Author information

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Abstract

The present work aimed to study some blood indices of rats as affected by saccharin and the therapeutic action of vitamins C and E. The used adult female Rattus norvegicus albino rats in the present study were weighing 100-120 g. Administration of saccharin at a dose of 35 mg kg body weight (b.wt.) day for 35 days significantly decreased serum glucose, triglycerides, cholesterol, total protein and albumin values. These decrements were by 20.16%, 22.76%, 44.92%, 20.16% and 40.44%, respectively, compared to control level (p value < 0.01). But it increased levels of kidney function indices. The effect of saccharin was more pronounced on creatinine. Activities of Alanine aminotranferease (ALT), aspartate aminotransferase (AST) and Alkaline phosphatase (ALP) increased significantly following saccharin treatment to rats. Concerning hematoligical parameters, the more obvious changes were observed in the increment of white blood cell (WBC), mean corpuscular volume (MCV) and platelets (PLT) and the decrease in hematocrit, hemoglobin (Hb) and red blood cells (RBCs) count in response to the administration of saccharin. In general, vitamin C or E (150 mg kg b.wt. day for 35 days) was able to reduce the effects of saccharin intake. Both vitamins, however, generally have beneficial effects in reducing the changes in the studied parameters.

http://www.ncbi.nlm.nih.gov/pubmed/20382728

the Islamic University of Gaza, Palestine

“It is estimated that sweetened beverages account for at least one-fifth of the weight gained between 1977 and 2007 in the US population.”

Public Health & Nutrition • March 2011

To what extent have sweetened beverages contributed to the obesity epidemic?

Author information

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Abstract

OBJECTIVE

A systematic literature review was conducted to determine whether sweetened beverage intake increases the risk for obesity, and the extent to which it has contributed to recent increases in energy intake and adiposity in the USA.

RESULTS

Obesity rates and sweetened beverage intake have increased in tandem in the USA. Studies consistently show that higher intake of sweetened beverages is associated with higher energy intake. Energy in liquid form is not well compensated for by reductions in the intake of other sources of energy. Well-designed observational studies consistently show a significant positive relationship between sweetened beverage intake and adiposity. More importantly, several well-conducted randomized controlled trials have shown statistically significant changes in adiposity as a result of corresponding changes in sweetened beverage intake.

CONCLUSIONS

All lines of evidence consistently support the conclusion that the consumption of sweetened beverages has contributed to the obesity epidemic. It is estimated that sweetened beverages account for at least one-fifth of the weight gained between 1977 and 2007 in the US population. Actions that are successful in reducing sweetened beverage consumption are likely to have a measurable impact on obesity.

http://www.ncbi.nlm.nih.gov/pubmed/20860886

“These results suggest that long-term consumption of Artificial Sweeteners might accelerate atherosclerosis and senescence ...”

Molecules And Cells • May 2011

Modified apolipoprotein (apo) A-I by artificial sweetener causes severe premature cellular senescence and atherosclerosis with impairment of functional and structural properties of apoA-I in lipid-free and lipid-bound state

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Abstract

Long-term consumption of artificial sweeteners (AS) has been the recent focus of safety concerns. However, the potential risk of the AS in cardiovascular disease and lipoprotein metabolism has not been investigated sufficiently. We compared the influence of AS (aspartame, acesulfame K, and saccharin) and fructose in terms of functional and structural correlations of apolipoprotein (apo) A-I and high-density lipoproteins (HDL), which have atheroprotective effects. Long-term treatment of apoA-I with the sweetener at physiological concentration (3 mM for 168 h) resulted in loss of antioxidant and phospholipid binding activities with modification of secondary structure. The AS treated apoA-I exhibited proteolytic cleavage to produce 26 kDa-fragment. They showed pro-atherogenic properties in acetylated LDL phagocytosis of macrophages. Each sweetener alone or sweetener-treated apoA-I caused accelerated senescence in human dermal fibroblasts. These results suggest that long-term consumption of AS might accelerate atherosclerosis and senescence via impairment of function and structure of apoA-I and HDL.

Full Text, Graphs, Charts and 40 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3887604/

“It can be concluded from these observations that long term consumption of aspartame leads to hepatocellular injury and alterations in liver antioxidant status ...”

Food And Chemical Toxicology • June 2011

Effect of long term intake of aspartame on antioxidant defense status in liver

Author information

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Abstract

The present study evaluates the effect of long term intake of aspartame, the artificial sweetener, on liver antioxidant system and hepatocellular injury in animal model. Eighteen adult male Wistar rats, weighing 150-175 g, were randomly divided into three groups as follows: first group was given aspartame dissolved in water in a dose of 500 mg/kg b.wt.; the second group was given a dose of 1000 mg/kg b.wt.; and controls were given water freely. Rats that had received aspartame (1000 mg/kg b.wt.) in the drinking water for 180 days showed a significant increase in activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and ß-glutamyl transferase (GGT). The concentration of reduced glutathione (GSH) and the activity of glutathione peroxidase (GPx), and glutathione reductase (GR) were significantly reduced in the liver of rats that had received aspartame (1000 mg/kg b.wt.). Glutathione was significantly decreased in both the experimental groups. Histopathological examination revealed leukocyte infiltration in aspartame-treated rats (1000 mg/kg b.wt.). It can be concluded from these observations that long term consumption of aspartame leads to hepatocellular injury and alterations in liver antioxidant status mainly through glutathione dependent system.

http://www.ncbi.nlm.nih.gov/pubmed/21376768

“... it would be worthwhile to investigate whether possible links between sucralose intake and Inflammatory Bowel Disease exist, before it is too late.”

Canadian Journal Of Gastroenterology • September 2011

What made Canada become a country with the highest incidence of inflammatory bowel disease: Could sucralose be the culprit?

By Xiaofa Qin, MD PhD, Department of Surgery, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ, USA

Abstract

Inflammatory bowel disease (IBD) (which includes both ulcerative colitis and Crohn’s disease [CD]) emerged and dramatically increased in the past century (1). Early studies revealed that IBD was most prevalent in countries such as the United Kingdom, the United States and those in northern Europe (1). Compared with these countries, the prevalence of IBD in Canada was much lower. This was demonstrated in early epidemiological studies conducted in Canada. According to a review by Mayberry and Rhodes (2), a study published in 1972 reported the incidence and prevalence of CD in Sherbrooke, Quebec, at only 0.7 and 6.3 per 100,000 population, respectively, which were much lower than countries such as the United Kingdom, the United States, Sweden, Denmark, and even Israel and New Zealand at the same time or even decades earlier. However, studies in recent years have suddenly found that Canada has become a country with the highest incidence of IBD (3). For example, the prevalence of CD in Alberta in 1981 was only 44 per 100,000 population (4), compared with 91 per 100,000 in Olmsted County, Minnesota (USA) on January 1, 1980 (5). However, the prevalence of CD in Alberta increased to 283 per 100,000 on July 1, 2000 (3), compared with 174 per 100,000 in Olmsted County in January 1, 2001 (6). It would be valuable to know what caused the dramatic increase of IBD in Canada because it may provide critical information regarding its etiology.

A decade ago, a series of accidental findings made me suspect that the impaired inactivation of digestive proteases due to the inhibition of gut bacteria by dietary chemicals, such as saccharin, play a causative role in IBD as a result of the accelerated degradation of the mucous layer and underlying endothelium (7). It provided an explanation for many puzzles in IBD such as the dramatic increase of IBD in the 1950s and 1960s, and its levelling off since the latter part of the 1970s, as observed in many western countries including Canada (4,7). However, this hypothesis was challenged by the failure to provide an explanation for the recent high incidence of IBD in Canada, which had adopted more stringent standards for the use of saccharin than most other western countries after the finding of carcinogenic effects of saccharin on the bladders of experimental animals in 1977. If not saccharin, then what caused the remarkable increase of IBD in Canada? I suggest that sucralose may be the culprit. Sucralose is a new, non-nutrient, high-intensity sweetener that has many superior properties. It is approximately 600 times sweeter than sucrose (thus two times sweeter than saccharin). Similar to saccharin, sucralose is heat and pH stable, but without the bitter aftertaste (8). In 1991, Canada was the first country to approve the use of sucralose, and it was allowed to be used as a tabletop sweetener in breakfast cereals, beverages, desserts, toppings, fillings, chewing gum, breath mints, fruit spreads, salad dressings, confectionary, bakery products, processed fruits and vegetables, alcoholic beverages, puddings and table syrups (8). Interestingly, the study by Wrobel et al (9) reported that the incidence of pediatric IBD in Southern Alberta was 2.3 (per 100,000 population) between 1983 and 1987, 2.5 between 1988 and 1992, 5.0 between 1993 and 1998, and 6.5 between 1999 and 2005 (9), indicating a dramatic increase in the early 1990s. Could sucralose cause the increase of IBD in Canada? How?

Similar to saccharin, sucralose can also exert potent inhibition of gut bacteria (10). However, it may have a more pronounced effect on gut bacteria than saccharin in that approximately 65% to 95% of sucralose is excreted through the feces unchanged (10), while a large proportion of saccharin is absorbed and eliminated through urine; the acceptable daily intake of sucralose is 15 mg/kg, but only 5 mg/kg for saccharin. As I suggested a decade ago, regarding the possible risk of saccharin on IBD (7), sucralose may have a similar but stronger impact on gut bacteria, digestive protease inactivation and gut barrier function. This may provide a possible explanation for the more pronounced high incidence of IBD observed in Canada. The use of sucralose is soaring, and is now being used in thousands of food products (10). Therefore, it would be worthwhile to investigate whether possible links between sucralose intake and IBD exist, before it is too late.

Full text with 10 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202359/

“... animal studies have convincingly proven that artificial sweeteners cause weight gain, brain tumors, bladder cancer and many other health hazards. Some kind of health related side effects including carcinogenicity are also noted in humans.”

Journal Of Pharmacology And Pharmacotherapy • October 2011

Sugar substitutes: Health controversy over perceived benefits

By KR Tandel
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Abstract

Sugar is an inseparable part of the food we consume. But too much sugar is not ideal for our teeth and waistline. There have been some controversial suggestions that excessive sugar may play an important role in certain degenerative diseases. So artificial sweeteners or artificially sweetened products continue to attract consumers. A sugar substitute (artificial sweetener) is a food additive that duplicates the effect of sugar in taste, but usually has less food energy. Besides its benefits, animal studies have convincingly proven that artificial sweeteners cause weight gain, brain tumors, bladder cancer and many other health hazards. Some kind of health related side effects including carcinogenicity are also noted in humans. A large number of studies have been carried out on these substances with conclusions ranging from “safe under all conditions” to “unsafe at any dose”. Scientists are divided in their views on the issue of artificial sweetener safety. In scientific as well as in lay publications, supporting studies are often widely referenced while the opposing results are de-emphasized or dismissed. So this review aims to explore the health controversy over perceived benefits of sugar substitutes.

Full text, graphs, charts and 54 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3198517/

“Our data suggest that acesulfame-K can be ingested by the prenatal or postnatal mice through their mother’s amniotic fluid or breast milk, producing a long-dated function on the adult’s sweet preference.”

Oxford Journal • Chemical Senses • November 2011

Effects of mother’s dietary exposure to acesulfame-K in Pregnancy or lactation on the adult offspring’s sweet preference

Author information
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Abstract

This study investigates whether mother’s exposure to the artificial sweetener acesulfame-K (AK) during pregnancy or lactation affected her adult offspring’s sweet preference. It was found that mother’s dietary exposure to AK in pregnancy or lactation decreased the preference thresholds for AK and sucrose solutions in the adult offspring, whereas the preference pattern and the most preferred concentration for AK or sucrose solution were unchanged. Furthermore, the preference scores in the exposure groups were increased significantly when compared with the control group at a range of concentrations for AK or sucrose solution. The existence of AK and its dynamic changes within 24 h in amniotic fluid during pregnancy or in mother’s milk during lactation after a single oral infusion of AK solution were revealed by the methods of reversed-phase high-performance liquid chromatography and mass spectrometry. Our data suggest that AK can be ingested by the prenatal or postnatal mice through their mother’s amniotic fluid or breast milk, producing a long-dated function on the adult’s sweet preference.

Full Text, Graphs, Charts and 34 References

http://chemse.oxfordjournals.org/content/36/9/763.long

“After 12 days, 30% of zebrafish, which consumed aspartame and high cholesterol diet, died with exhibiting swimming defects ... aspartame-fed zebrafish exhibited acute swimming defects with an increase in brain inflammation.”

Food Chemical Toxicology • November 2011

Aspartame-fed zebrafish exhibit acute deaths with swimming defects and saccharin-fed zebrafish have elevation of cholesteryl ester transfer protein activity in hypercholesterolemia

Author information
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Abstract

Although many artificial sweeteners (AS) have safety issues, the AS have been widely used in industry. To determine the physiologic effect of AS in the presence of hyperlipidemia, zebrafish were fed aspartame or saccharin with a high-cholesterol diet (HCD). After 12 days, 30% of zebrafish, which consumed aspartame and HCD, died with exhibiting swimming defects. The aspartame group had 65% survivability, while the control and saccharin groups had 100% survivability. Under HCD, the saccharin-fed groups had the highest increase in the serum cholesterol level (599 mg/dL). Aspartame-fed group showed a remarkable increase in serum glucose (up to 125 mg/dL), which was 58% greater than the increase in the HCD alone group. The saccharin and HCD groups had the highest cholesteryl ester transfer protein (CETP) activity (52% CE-transfer), while the HCD alone group had 42% CE-transfer. Histologic analysis revealed that the aspartame and HCD groups showed more infiltration of inflammatory cells in the brain and liver sections. Conclusively, under presence of hyperlipidemia, aspartame-fed zebrafish exhibited acute swimming defects with an increase in brain inflammation. Saccharin-fed zebrafish had an increased atherogenic serum lipid profile with elevation of CETP activity.

http://www.ncbi.nlm.nih.gov/pubmed/21855599

International Journal Of Occupational And Environmental Health • January 2010

Inadequate toxicity tests of food additive acesulfame

Author information

By M. Karstadt

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Abstract

“Despite poor-quality toxicity tests, acesulfame potassium was approved by the US Food and Drug Administration (FDA) for use as an artificial sweetener. At present, acesulfame is very widely used, most frequently in blends with the most popular artificial sweetener in the US, sucralose (Splenda). Acesulfame was nominated twice (in 1996 and again in 2006) for testing in the National Toxicology Program (NTP) bioassay program. Both nominations were rejected by NTP. Rather than carry out bioassays, NTP subjected acesulfame to tests in genetically modified mice (GMM). Those GMM tests yielded results that provided no insight into potential carcinogenicity of acesulfame. It is possible that FDA discouraged NTP from conducting bioassays of acesulfame. Acesulfame should be tested in the bioassay program as soon as possible, and steps should be taken to ensure the objectivity of the bioassay nomination process.”

http://www.ncbi.nlm.nih.gov/pubmed/20166324

“... chronically high consumption of fructose in rodents leads to hepatic and extrahepatic insulin resistance, obesity, type 2 diabetes mellitus, and high blood pressure.”

Physiology Reviews • January 2010

Metabolic effects of fructose and the worldwide increase in obesity

Author information

Tappy L1, Lê KA.

Abstract

While virtually absent in our diet a few hundred years ago, fructose has now become a major constituent of our modern diet. Our main sources of fructose are sucrose from beet or cane, high fructose corn syrup, fruits, and honey. Fructose has the same chemical formula as glucose (C(6)H(12)O(6)), but its metabolism differs markedly from that of glucose due to its almost complete hepatic extraction and rapid hepatic conversion into glucose, glycogen, lactate, and fat. Fructose was initially thought to be advisable for patients with diabetes due to its low glycemic index. However, chronically high consumption of fructose in rodents leads to hepatic and extrahepatic insulin resistance, obesity, type 2 diabetes mellitus, and high blood pressure. The evidence is less compelling in humans, but high fructose intake has indeed been shown to cause dyslipidemia and to impair hepatic insulin sensitivity. Hepatic de novo lipogenesis and lipotoxicity, oxidative stress, and hyperuricemia have all been proposed as mechanisms responsible for these adverse metabolic effects of fructose. Although there is compelling evidence that very high fructose intake can have deleterious metabolic effects in humans as in rodents, the role of fructose in the development of the current epidemic of metabolic disorders remains controversial. Epidemiological studies show growing evidence that consumption of sweetened beverages (containing either sucrose or a mixture of glucose and fructose) is associated with a high energy intake, increased body weight, and the occurrence of metabolic and cardiovascular disorders. There is, however, no unequivocal evidence that fructose intake at moderate doses is directly related with adverse metabolic effects. There has also been much concern that consumption of free fructose, as provided in high fructose corn syrup, may cause more adverse effects than consumption of fructose consumed with sucrose. There is, however, no direct evidence for more serious metabolic consequences of high fructose corn syrup versus sucrose consumption.

Full text, great images, graphs and charts with 246 references

http://physrev.physiology.org/content/90/1/23.long

Currents In Hypertension Reports • April 2010

The role of high-fructose corn syrup in metabolic syndrome and hypertension

Author information

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Abstract

"Obesity and related diseases are an important and growing health concern in the United States and around the world. Soft drinks and other sugar-sweetened beverages are now the primary sources of added sugars in Americans' diets. The metabolic syndrome is a cluster of common pathologies, including abdominal obesity linked to an excess of visceral fat, fatty liver, insulin resistance, hyperinsulinemia, dyslipidemia, and hypertension. Trends in all of these alterations are related to the consumption of dietary fructose and the introduction of high-fructose corn syrup (HFCS) as a sweetener in soft drinks and other foods. Experimental and clinical evidence suggests a progressive association between HFCS consumption, obesity, and the other injury processes. However, experimental HFCS consumption seems to produce some of the changes associated with metabolic syndrome even without increasing the body weight. Metabolic damage associated with HFCS probably is not limited to obesity-pathway mechanisms."

http://www.ncbi.nlm.nih.gov/pubmed/20424937

Yale Journal Of Biology And Medicine • June 2010

Gain weight by "going diet?"
Artificial sweeteners and the neurobiology of sugar cravings: Neuroscience 2010

By Dr. Q. Yang
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Abstract

America's obesity epidemic has gathered much media attention recently. A rise in the percent of the population who are obese coincides with an increase in the widespread use of non-caloric artificial sweeteners, such as aspartame (e.g., Diet Coke) and sucralose (e.g., Pepsi One), in food products (Figure 1). Both forward and reverse causalities have been proposed. While people often choose "diet" or "light" products to lose weight, research studies suggest that artificial sweeteners may contribute to weight gain. In this mini-review, inspired by a discussion with Dr. Dana Small at Yale's Neuroscience 2010 conference in April, I first examine the development of artificial sweeteners in a historic context. I then summarize the epidemiological and experimental evidence concerning their effects on weight. Finally, I attempt to explain those effects in light of the neurobiology of food reward.

Full Text with 57 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2892765/

“frequent consumption of infusions ... [of] potatoes, alcohol, sweets, and processed meat resulted in a high risk for urinary tract tumors”

European Journal Of Cancer Prevention • November 2010

Dietary patterns and food groups are linked to the risk of urinary tract tumors in Argentina

Author information

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Abstract

Epidemiological and laboratory research has shown that dietary components are associated with the risk of developing urinary tract tumors (UTT). The purpose of this case-control study, carried out between 2004 and 2008 in Córdoba, a Mediterranean city in Argentina, was to describe the role of dietary patterns and to investigate any association with the risk of developing UTT. One hundred and sixty-eight patients with histologically confirmed transitional UTT and 334 controls with acute, nonneoplastic, and nonurinary tract diseases from the same hospitals were studied. All patients were interviewed about their food habits and their exposure to a number of known or suspected risk factors for UTT. Multiple correspondence analysis was used to explore dietary patterns and data analyses were carried out by calculating odds ratios and their 95% confidence intervals by using multiple logistic regression. Two main dietary patterns identified were a ‘prudent’ pattern that was linked to controls and a ‘western’ pattern that was associated with cases. A frequent intake of vegetable oils, lean meats, grains, and fruits, the moderate use of alcohol (mainly red wine) together with potato and sweet consumption, and the habit of taking at least four meals per day, were associated with a reduced risk for UTT. In contrast, frequent consumption of infusions (mainly maté), potatoes, alcohol, sweets, and processed meat resulted in a high risk for UTT. The dietary patterns of our population have a role in the development of UTT, thus implying that appropriate nutritional education may decrease this risk.

http://www.ncbi.nlm.nih.gov/pubmed/20736839

“Consumption of sweetened beverages is however clearly associated with excess calorie intake, and an increased risk of diabetes and cardiovascular diseases through an increase in body weight.”

Nutrition • November 2010

Fructose and metabolic diseases: new findings, new questions

Author information

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Abstract

There has been much concern regarding the role of dietary fructose in the development of metabolic diseases. This concern arises from the continuous increase in fructose (and total added caloric sweeteners consumption) in recent decades, and from the increased use of high-fructose corn syrup (HFCS) as a sweetener. A large body of evidence shows that a high-fructose diet leads to the development of obesity, diabetes, and dyslipidemia in rodents. In humans, fructose has long been known to increase plasma triglyceride concentrations. In addition, when ingested in large amounts as part of a hypercaloric diet, it can cause hepatic insulin resistance, increased total and visceral fat mass, and accumulation of ectopic fat in the liver and skeletal muscle. These early effects may be instrumental in causing, in the long run, the development of the metabolic syndrome. There is however only limited evidence that fructose per se, when consumed in moderate amounts, has deleterious effects. Several effects of a high-fructose diet in humans can be observed with high-fat or high-glucose diets as well, suggesting that an excess caloric intake may be the main factor involved in the development of the metabolic syndrome. The major source of fructose in our diet is with sweetened beverages (and with other products in which caloric sweeteners have been added). The progressive replacement of sucrose by HFCS is however unlikely to be directly involved in the epidemy of metabolic disease, because HFCS appears to have basically the same metabolic effects as sucrose. Consumption of sweetened beverages is however clearly associated with excess calorie intake, and an increased risk of diabetes and cardiovascular diseases through an increase in body weight. This has led to the recommendation to limit the daily intake of sugar calories.

http://www.ncbi.nlm.nih.gov/pubmed/20471804

“The consumption of breakfast outside the home, soft drinks and energy-dense fast foods were positively associated with overweight and obesity in adolescents.”

Asia Pacific Journal Of Clinical Nutrition • December 2010

Dietary habits and overweight/obesity in adolescents in Xi’an City, China

Author information

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Abstract

This study explored the association between dietary habits and overweight and obesity in adolescents from Xi’an City, China. A cross-sectional sample of 1804 adolescents was recruited in 2004 from 30 junior high schools in six districts of Xi’an City, northwest China. Weight and height was measured and eating habits assessed using a self-administered questionnaire. Logistic regression was used to identify dietary patterns associated with overweight and obesity and adjusted for socio-demographic factors. Consumption of foods and beverages outside three main meals, and potato chips was more popular in boys than in girls, while girls consumed more fried food and soft drinks than boys. In boys, an increased consumption of soft drinks was associated with increased risk of overweight and obesity (1100 mL/day, OR: 1.9, 95% CI: 1.1-3.8), while consuming preserved fruit was associated with decreased risk (OR: 0.6, 95% CI: 0.5-0.9). In girls, having breakfast outside the home (OR: 1.7, 95% CI: 1.1-2.3) and an increased consumption of energy-dense foods (OR: 1.7, 95% CI: 1.04-2.9), was associated with increased risk of overweight and obesity, while frequently having foods and beverages outside the three main meals (OR: 0.6, 95% CI: 0.4-0.9) was associated with decreased risk. The consumption of breakfast outside the home, soft drinks and energy-dense fast foods were positively associated with overweight and obesity in adolescents. Future health education programs to prevent excess weight gain should target such unhealthy eating habits.

Full text in both English and Chinese versions, graphs and 23 references

http://apjcn.nhri.org.tw/server/APJCN/19/1/76.pdf

“Consumption of sweeteners
[saccharin, cyclamate based, acesulfame-K based, and aspartame]
resulted in significantly increased body weight; however, the food intake did not change.
These results question the effect of non-caloric artificial sweeteners
on weight-maintenance or body weight decrease.”

Acta Physiologica Hungarica • December 2010

Effects of artificial sweeteners on body weight, food and drink intake

Author information
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Abstract

Artificial sweeteners are widely used all over the world. They may assist in weight management, prevention of dental caries, control of blood glucose of diabetics, and also can be used to replace sugar in foods. In the animal experimentation mice were given oral doses of water solutions of table top artificial sweeteners (saccharin, cyclamate based, acesulfame-K based, and aspartame) the amount of maximum Acceptable Daily Intake (ADI) ad libitum. The controls received only tap water with the same drinking conditions as the treated groups. The mice were fed chow ad libitum. We measured food intake and body weight once a week, water and solutions of artificial sweeteners intake twice a week. The data were analysed by statistical methods (T-probe, regression analysis). Consumption of sweeteners resulted in significantly increased body weight; however, the food intake did not change. These results question the effect of non-caloric artificial sweeteners on weight-maintenance or body weight decrease.

http://www.ncbi.nlm.nih.gov/pubmed/21138816

“The addition of Non-nutritive sweeteners to diets poses no benefit for weight loss or reduced weight gain without energy restriction. There are long-standing and recent concerns that inclusion of Non-nutritive sweeteners in the diet promotes energy intake and contributes to obesity.”

American Journal Of Clinical Nutrition • January 2009

Non-nutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms

Author information

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Abstract

Non-nutritive sweeteners (NNS) are ecologically novel chemosensory signaling compounds that influence ingestive processes and behavior. Only about 15% of the US population aged >2 y ingest NNS, but the incidence is increasing. These sweeteners have the potential to moderate sugar and energy intakes while maintaining diet palatability, but their use has increased in concert with BMI in the population. This association may be coincidental or causal, and either mode of directionality is plausible. A critical review of the literature suggests that the addition of NNS to non-energy-yielding products may heighten appetite, but this is not observed under the more common condition in which NNS is ingested in conjunction with other energy sources. Substitution of NNS for a nutritive sweetener generally elicits incomplete energy compensation, but evidence of long-term efficacy for weight management is not available. The addition of NNS to diets poses no benefit for weight loss or reduced weight gain without energy restriction. There are long-standing and recent concerns that inclusion of NNS in the diet promotes energy intake and contributes to obesity. Most of the purported mechanisms by which this occurs are not supported by the available evidence, although some warrant further consideration. Resolution of this important issue will require long-term randomized controlled trials.

Full text, graphs, charts and 224 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2650084/

“Overweight occurs frequently among Jamaican 15-19-year-olds and is associated with increased consumption of sweetened beverages. High Waist Circumference is more prevalent among females and is related to low consumption of fruits and vegetables.”

Public Health Nutrition • August 2009

Fast-food and sweetened beverage consumption: association with overweight and high waist circumference in adolescents

Author information

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Abstract

OBJECTIVE

Overweight and obesity have increased to epidemic proportions among adolescents and are associated with chronic non-communicable diseases and excess mortality in adulthood. The association of overweight/obesity with poor dietary habits has not been studied in adolescents in middle-income developing countries. The present study aimed to estimate the prevalence of overweight, obesity and high waist circumference (WC) in 15-19-year-old Jamaican adolescents and to investigate the association with fast-food and sweetened beverage consumption.

DESIGN

The study enrolled 1317 (598 male, 719 female) adolescents aged 15-19 years using multistage, nationally representative sampling. Age-specific prevalence calculation used internal Z-score lines connecting with the WHO adult cut-off points. Logistic regression was used to examine the association of overweight or high WC with fast-food and sweetened beverage consumption, adjusting for potential confounders.

RESULTS

The overall prevalence of overweight, obesity and high WC was approximately 15 %, 6 % and 10 %, respectively. Prevalence estimated using internal Z-scores was similar to that using the International Obesity Taskforce cut-off points. Obesity (8.0 % in females, 3.3 % in males) and high WC (16.2 % in females, 1.7 % in males) were significantly more prevalent in females when using internal Z-score cut-offs. High WC was associated with the absence of fruit consumption ($P = 0.043$) and overweight with high sweetened beverage consumption ($P = 0.018$).

CONCLUSION

Overweight occurs frequently among Jamaican 15-19-year-olds and is associated with increased consumption of sweetened beverages. High WC is more prevalent among females and is related to low consumption of fruits and vegetables. Measures to reduce the consumption of sweetened beverages and increase fruit intake may reduce the prevalence of excess body fat among adolescents.

http://www.ncbi.nlm.nih.gov/pubmed/19243675

“Aspartame had a vestibulocochlear toxicity in a pair of siblings, suggesting a genetic susceptibility to aspartame toxicity. Even though the yield may be low, asking patients with dizziness, vertigo, tinnitus, or high-frequency hearing loss about their aspartame consumption and suggesting cessation of its use, may prove helpful for some.”

Cases Journal • September 2009

Vestibulocochlear toxicity in a pair of siblings 15 years apart secondary to aspartame: two case reports

Author information
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Abstract

INTRODUCTION

Aspartame may have idiosyncratic toxic effects for some people; however, there are few case reports published in the medical literature. We present two case reports in a pair of siblings, one with a vestibular and the other with a cochlear toxicity to aspartame. The cochlear toxicity is the first case to be reported, while the vestibular toxicity is the second case to be reported.

CASE PRESENTATION

A 29-year-old white female had a 20-month history of nausea and headache, progressively getting worse with time and eventually to also involve vomiting, vertigo, and ataxia. She was extensively evaluated and diagnosed with a vestibular neuronitis versus a chronic labyrinthitis and treated symptomatically with limited success. In response to a newspaper article, she stopped her aspartame consumption with total cessation of her symptoms. Fifteen years later, her then 47-year-old white brother had a 30-month history of an intermittent, initially 5-10 minute long episode of a mild sensorineural hearing loss in his right ear that progressed over time to several hour episodes of a moderately severe high-frequency sensorineural hearing loss to include tinnitus and a hypoesthetic area in front of his right tragus. After a negative magnetic resonance scan of the brain, he remembered his sister’s experience with aspartame and stopped his consumption of aspartame with resolution of his symptoms, although the very high frequency hearing loss took at least 15 months to resolve. For both, subsequent intentional challenges with aspartame and unintentional exposures brought back each of their respective symptoms.

CONCLUSION

Aspartame had a vestibulocochlear toxicity in a pair of siblings, suggesting a genetic susceptibility to aspartame toxicity. Even though the yield may be low, asking patients with dizziness, vertigo, tinnitus, or high-frequency hearing loss about their aspartame consumption and suggesting cessation of its use, may prove helpful for some.

Full text with graphs, charts and references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2815650/

Basic Clinical Pharmacology And Toxicology • February 2008

Consequences of exposure to carcinogens beginning during developmental life

Author information

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Abstract

The increased incidence of cancer over the last 50-60 years may be largely attributed to two factors: the ageing of the population and the diffusion of agents and situations presenting carcinogenic risks. Today, we have entered into a new era in which populations are ever-increasingly exposed to diffuse carcinogenic risks, present not only in the occupational, but also in the general environment. We must now also consider an additional factor in the carcinogenic process, that is, the age in which exposure to carcinogenic risks begins. Apart from the paradigmatic cases of diethylstilboestrol and ionizing radiation, the available epidemiological data concerning the adult consequences of developmental exposure to carcinogens is very limited. However, important data have been provided by long-term experimental carcinogenicity bioassays conducted using rodents. This paper reports a selection of studies conducted in the laboratories of the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation in which exposure to the chemical agents vinyl acetate monomer, ethyl alcohol and aspartame was started during developmental life and continued into adulthood. The results of these studies provide supporting evidence that lifespan exposure to carcinogenic agents beginning during developmental life produces an overall increase in the carcinogenic effects observed. Moreover, when comparing prenatal and postnatal exposure, the data demonstrate that the development of cancers may appear earlier in life.

Full text, graphs, charts and 14 references

http://onlinelibrary.wiley.com/doi/10.1111/j.1742-7843.2007.00200.x/epdf

“This paper reports a selection of studies conducted in the laboratories of the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation in which exposure to the chemical agents vinyl acetate monomer, ethyl alcohol and aspartame was started during developmental life and continued into adulthood. The results of these studies provide supporting evidence that lifespan exposure to carcinogenic agents beginning during developmental life produces an overall increase in the carcinogenic effects observed. Moreover, when comparing prenatal and postnatal exposure, the data demonstrate that the development of cancers may appear earlier in life.”

The Journal Of School Nursing • February 2008

The role of sugar-sweetened beverage consumption in adolescent obesity: a review of the literature

By S. Harrington
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Abstract

Soft drink consumption has increased by 300% in the past 20 years, and 56-85% of children in school consume at least one soft drink daily. The odds ratio of becoming obese among children increases 1.6 times for each additional can or glass of sugar-sweetened drink consumed beyond their usual daily intake of the beverage. Soft drinks currently constitute the leading source of added sugars in the diet and exceed the U.S. Department of Agriculture's recommended total sugar consumption for adolescents. With the increase in adolescent obesity and the concurrent increase in consumption of sugar-sweetened beverages (SSB), the assumption infers a relationship between the two variables. SSB, classified as high-glycemic index (GI) liquids, increase postprandial blood glucose levels and decrease insulin sensitivity. Additionally, high-GI drinks submit to a decreased satiety level and subsequent overeating. Low-GI beverages stimulate a delayed return of hunger, thereby prompting an increased flexibility in amounts and frequencies of servings. Single intervention manipulation, elimination, or marked reduction of SSB consumption may serve to decrease caloric intake, increase satiety levels, decrease tendencies towards insulin resistance, and simplify the process of weight management in this population.

http://www.ncbi.nlm.nih.gov/pubmed/18220450

"The odds ratio of becoming obese among children increases 1.6 times for each additional can or glass of sugar-sweetened drink consumed beyond their usual daily intake of the beverage.

Soft drinks currently constitute the leading source of added sugars in the diet and exceed the U.S. Department of Agriculture's recommended total sugar consumption for adolescents."

“The comet parameters of DNA were increased in the bone marrow cells due to the sweetener-induced DNA strand breaks, as revealed by increased comet-tail extent and percent DNA in the tail. Acesulfame K and saccharin were found to induce greater DNA damage than Aspartame.”

Drug Chemistry And Toxicology • April 2008

Genotoxicity testing of low-calorie sweeteners: aspartame, acesulfame-K, and saccharin

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Abstract

Low-calorie sweeteners are chemicals that offer the sweetness of sugar without the calories. Consumers are increasingly concerned about the quality and safety of many products present in the diet, in particular, the use of low-calorie sweeteners, flavorings, colorings, preservatives, and dietary supplements. In the present study, we evaluated the mutagenicity of the three low-calorie sweeteners in the Ames/Salmonella/microsome test and their genotoxic potential by comet assay in the bone marrow cells of mice. Swiss albino mice, Mus musculus, were orally administered with different concentrations of aspartame (ASP; 7, 14, 28, and 35 mg/kg body weight), acesulfame-K (ASK; 150, 300, and 600 mg/kg body weight), and saccharin (50, 100, and 200 mg/kg body weight) individually. Concurrently negative and positive control sets were maintained. The animals were sacrificed and the bone marrow cells were processed for comet assay. The standard plate-incorporation assay was carried with the three sweeteners in Salmonella typhimurium TA 97a and TA 100 strains both in the absence and presence of the S9 mix. The comet parameters of DNA were increased in the bone marrow cells due to the sweetener-induced DNA strand breaks, as revealed by increased comet-tail extent and percent DNA in the tail. ASK and saccharin were found to induce greater DNA damage than ASP. However, none could act as a potential mutagen in the Ames/Salmonella /microsome test. These findings are important, since they represent a potential health risk associated with the exposure to these agents.

http://www.ncbi.nlm.nih.gov/pubmed/18850355

“We propose that excessive aspartame ingestion might be involved in the pathogenesis of certain mental disorders (DSM-IV-TR 2000) and also in compromised learning and emotional functioning.”

European Journal Of Clinical Nutrition • April 2008

Direct and indirect cellular effects of aspartame on the brain

Author information

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Abstract

The use of the artificial sweetener, aspartame, has long been contemplated and studied by various researchers, and people are concerned about its negative effects. Aspartame is composed of phenylalanine (50%), aspartic acid (40%) and methanol (10%). Phenylalanine plays an important role in neurotransmitter regulation, whereas aspartic acid is also thought to play a role as an excitatory neurotransmitter in the central nervous system. Glutamate, asparagines and glutamine are formed from their precursor, aspartic acid. Methanol, which forms 10% of the broken down product, is converted in the body to formate, which can either be excreted or can give rise to formaldehyde, diketopiperazine (a carcinogen) and a number of other highly toxic derivatives. Previously, it has been reported that consumption of aspartame could cause neurological and behavioural disturbances in sensitive individuals. Headaches, insomnia and seizures are also some of the neurological effects that have been encountered, and these may be accredited to changes in regional brain concentrations of catecholamines, which include norepinephrine, epinephrine and dopamine. The aim of this study was to discuss the direct and indirect cellular effects of aspartame on the brain, and we propose that excessive aspartame ingestion might be involved in the pathogenesis of certain mental disorders (DSM-IV-TR 2000) and also in compromised learning and emotional functioning.

http://www.ncbi.nlm.nih.gov/pubmed/17684524

Cancer Epidemiology, Biomarkers & Prevention • May 2008

Aspartame and Incidence of Brain Malignancies

By Devra Lee Davis, Leanne Ganter and Jonathan Weinkle

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University of Pittsburgh Cancer Institute, Center for Environmental Oncology
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To the Editors:

Lim et al. (1) found no relationship between the "Consumption of aspartame-containing beverages and incidence of hematopoietic and brain malignancies" by surveying retired individuals about their consumption of diet sodas and determining whether they had an increase in brain tumors 5 years later. In fact, this study design was not able to test the hypothesized relationship because it did not assess all exposures to aspartame and because it only evaluated short-term exposures in older adults.

Lim et al. estimated average daily aspartame consumption values based solely on the consumption of beverages containing aspartame. Lim et al. states that 70% of consumed aspartame is obtained through diet beverages, citing the American Dietetic Association as the source of this information. The American Dietetic Association, in turn, cites Equal.com, a large supplier of aspartame-containing products, as the authority for their statement; when contacted for corroborating information, Equal.com could not provide this corroboration. According to the Aspartame Information Center, more dry products contain aspartame than do drink products. The Lim et al. study assumed that the average daily intake of aspartame was equivalent to approximately one 12-oz. can of diet soda and did not include products, such as table sugars, candies, yogurt, nutrition bars, and even chewing gum (2).

Table 1. Average daily intake of aspartame

Substance	Quantity per day	Concentration of aspartame consumed (mg)
Diet soda (200 mg/can)	2 cans	400
Yogurt (125 mg/yogurt)	2 yogurts	250
Diet custard/pudding (75 mg/mouse)	1 serving	75
Coffee with sweetener (40/mg packet)	4 cups	160
Candy/chewing gum (2.5/candy)	10 candies	25
Totals		910

Table 1 , from the European Ramazzini Foundation, estimates the average daily amount of aspartame consumed from some of the most commonly used products out of the more than 6,000 in which it is present (3). If a woman ate these foods and weighed 60 kg (~132 lb), she would consume an aspartame daily dose of 15.1 mg/kg of body weight; a child weighing 30 kg (~66 lb) with a similar daily intake would have an aspartame daily dose twice as high—30.3 mg/kg of body weight (4). This estimated average daily level is well above the dose that was examined in Lim et al.'s study. See Table 1, Average daily intake of aspartame.

For those who are dieting, daily consumption of aspartame can be considerably higher. For instance, the South Beach Diet attempts to eliminate sugar intake by endorsing the extensive use of sugar substitutes, such as aspartame (5). Despite its popularity in various diet programs, research does not indicate that aspartame promotes weight loss, and some report that it functions as an appetite stimulant (6).

The Lim et al. study included members of the AARP of ages 50 to 71 years. Aspartame was not approved by the Food and Drug Administration as a food additive until July 1981. The population of the Lim et al. study grew during a period when aspartame use was considerably less than it is now, and none would have consumed aspartame as children (7). Aspartame is now used in countless consumer products, some we may not even be aware of, and is consumed by about 200 million Americans every day. In America today, more than 10 million children regularly consume sodas and other foods containing aspartame. This study cannot evaluate the possibility that infants and children whose exposures can begin in utero and young persons who can drink several sodas a day will incur a greater risk of brain and other cancers when they reach the older ages.

The greater vulnerability of the young to carcinogens has consistently been shown experimentally for aspartame and a number of other compounds (8). Some experimental studies have not found a connection to brain malignancies and aspartame consumption in rats (9). But these studies ended after 2 years. In a rodent, 2 years cor-

responds to about 60 years in humans, and more and more of the population are living into their 80s. The Ramazzini Foundation relies on a lifespan protocol in which rodents live their entire life span and are examined for signs of tumors or other damage upon natural death or by the end of the third year. Soffritti's September 2007 publication (10) supported the 2005 (11) experiment that found an obvious association between aspartame and multiple types of cancers. Animals exposed prenatally to aspartame in this latest work have double the risk of multiple tumors compared with those exposed postnatally.

In light of these experimental findings, in evaluating public health effects of widely used materials, it is important to consider information on lifetime exposures, especially those that may begin prenatally. The possible effect of full lifetime and prenatal exposures on humans of aspartame cannot be evaluated in the Lim et al. study population, which only examined persons exposed as adults to aspartame.

More than half of all Americans are estimated to use aspartame every day, including many pregnant women and children. The negative findings in the Lim et al. study do not prove that there are no long-term effects of aspartame. The older study population analyzed and the limited ingestion of aspartame evaluated cannot reflect the long-term public-health effects of aspartame that may begin prenatally and run throughout a lifetime. In light of the limited nature of the study by Lim et al. and recent reports of Soffritti finding that aspartame significantly increases the risks of tumors in rodents, with a doubled risk in those in which exposures begin prenatally, the Food and Drug Administration should review its approval of aspartame.

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Full text and references: http://cebp.aacrjournals.org/content/17/5/1295.full.pdf

“Regular use of artificial sweeteners for 10 years or more was positively associated with urinary tract tumors.”

Preventive Medicine • July 2008

Artificial sweetener consumption and urinary tract tumors in Cordoba, Argentina

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Abstract

OBJECTIVE

To determine the role of the habitual use of the most common artificial sweeteners (AS) in the development of urinary tract tumors (UTT) in Argentina.

METHODS

Case-control study of 197 patients with histologically confirmed UTT of transitional varieties, and 397 controls with acute, non-neoplastic, and non-urinary tract diseases, admitted to the same hospitals in Córdoba (Argentina) between 1999 and 2006. All subjects were interviewed about their use of AS and their exposure to other known or suspected risk factors for UTT.

RESULTS

Fifty-one UTT patients (26%) and 87 controls (22%) used AS. The risk of UTT was significantly increased in long-term (> or =10 years) AS users compared with none-AS users. The OR (95% CI) for long-term consumers was 2.18 (1.22-3.89) and for short-term users was 1.10 (0.61-2.00) after adjustment for age, gender, BMI, social status. and years of tobacco use.

CONCLUSION

Regular use of AS for 10 years or more was positively associated with UTT.

http://www.ncbi.nlm.nih.gov/pubmed/18495230

“Regular consumption of sugar-sweetened soft drinks and fruit drinks is associated with an increased risk of type 2 diabetes mellitus in African American women.”

Archives In Internal Medicine • July 2008

Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women

By Palmer JR1, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L.

Abstract

BACKGROUND

Type 2 diabetes mellitus is an increasingly serious health problem among African American women. Consumption of sugar-sweetened drinks was associated with an increased risk of diabetes in 2 studies but not in a third; however, to our knowledge, no data are available on African Americans regarding this issue. Our objective was to examine the association between consumption of sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes mellitus in African American women.

METHODS

A prospective follow-up study of 59,000 African American women has been in progress since 1995. Participants reported on food and beverage consumption in 1995 and 2001. Biennial follow-up questionnaires ascertained new diagnoses of type 2 diabetes. The present analyses included 43,960 women who gave complete dietary and weight information and were free from diabetes at baseline. We identified 2713 incident cases of type 2 diabetes mellitus during 338,884 person-years of follow-up. The main outcome measure was the incidence of type 2 diabetes mellitus.

RESULTS

The incidence of type 2 diabetes mellitus was higher with higher intake of both sugar-sweetened soft drinks and fruit drinks. After adjustment for confounding variables including other dietary factors, the incidence rate ratio for 2 or more soft drinks per day was 1.24 (95% confidence interval, 1.06-1.45). For fruit drinks, the comparable incidence rate ratio was 1.31 (95% confidence interval, 1.13-1.52). The association of diabetes with soft drink consumption was almost entirely mediated by body mass index, whereas the association with fruit drink consumption was independent of body mass index.

CONCLUSIONS

Regular consumption of sugar-sweetened soft drinks and fruit drinks is associated with an increased risk of type 2 diabetes mellitus in African American women. While there has been increasing public awareness of the adverse health effects of soft drinks, little attention has been given to fruit drinks, which are often marketed as a healthier alternative to soft drinks.

Full text with graphs, charts and 25 references

Link: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2708080/

“... the intake of acesulfame K approached the average daily intake for small children and the total intake of benzoic acid was increased to above the average daily intake for most age groups. The highest intake of benzoic acid was observed for 1- to 2-year-old children, and benzoic acid intake in Norwegian children is therefore considered to be of special concern.”

Food And Chemical Toxicology • September 2008

Reducing added sugar intake in Norway by replacing sugar sweetened beverages with beverages containing intense sweeteners - a risk benefit assessment

Author information

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Abstract

A risk benefit assessment in Norway on the intake of added sugar, intense sweeteners and benzoic acid from beverages, and the influence of changing from sugar sweetened to diet beverages was performed. National dietary surveys were used in the exposure assessment, and the content of added sugar and food additives were calculated based on actual contents used in beverages and sales volumes provided by the manufactures. The daily intake of sugar, intense sweeteners and benzoic acid were estimated for children (1- to 13-years-old) and adults according to the current intake level and a substitution scenario where it was assumed that all consumed beverages contained intense sweeteners. The change from sugar sweetened to diet beverages reduced the total intake of added sugar for all age groups but especially for adolescent. This change did not result in intake of intense sweeteners from beverages above the respective ADIs. However, the intake of acesulfame K approached ADI for small children and the total intake of benzoic acid was increased to above ADI for most age groups. The highest intake of benzoic acid was observed for 1- to 2-year-old children, and benzoic acid intake in Norwegian children is therefore considered to be of special concern.

http://www.ncbi.nlm.nih.gov/pubmed/18639604

AAOHN Journal • June 2008

The potential toxicity of artificial sweeteners

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Abstract

Since their discovery, the safety of artificial sweeteners has been controversial. Artificial sweeteners provide the sweetness of sugar without the calories. As public health attention has turned to reversing the obesity epidemic in the United States, more individuals of all ages are choosing to use these products. These choices may be beneficial for those who cannot tolerate sugar in their diets (e.g., diabetics). However, scientists disagree about the relationships between sweeteners and lymphomas, leukemias, cancers of the bladder and brain, chronic fatigue syndrome, Parkinson's disease, Alzheimer's disease, multiple sclerosis, autism, and systemic lupus. Recently these substances have received increased attention due to their effects on glucose regulation. Occupational health nurses need accurate and timely information to counsel individuals regarding the use of these substances. This article provides an overview of types of artificial sweeteners, sweetener history, chemical structure, biological fate, physiological effects, published animal and human studies, and current standards and regulations.

http://www.ncbi.nlm.nih.gov/pubmed/18604921

"... scientists disagree about the relationships between sweeteners and lymphomas, leukemias, cancers of the bladder and brain, chronic fatigue syndrome, Parkinson's disease, Alzheimer's disease, multiple sclerosis, autism, and systemic lupus. Recently these substances have received increased attention due to their effects on glucose regulation. Occupational health nurses need accurate and timely information to counsel individuals regarding the use of these substances. This article provides an overview of types of artificial sweeteners, sweetener history, chemical structure, biological fate, physiological effects, published animal and human studies, and current standards and regulations."

“Acesulfame-K and saccharin were found to induce greater DNA damage than aspartame ... These findings are important, since they represent a potential health risk associated with the exposure to these agents.”

Drug And Chemical Toxicology • December 2008

Genotoxicity testing of low-calorie sweeteners: aspartame, acesulfame-K, and saccharin

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Abstract

Low-calorie sweeteners are chemicals that offer the sweetness of sugar without the calories. Consumers are increasingly concerned about the quality and safety of many products present in the diet, in particular, the use of low-calorie sweeteners, flavorings, colorings, preservatives, and dietary supplements. In the present study, we evaluated the mutagenicity of the three low-calorie sweeteners in the Ames/Salmonella/microsome test and their genotoxic potential by comet assay in the bone marrow cells of mice. Swiss albino mice, Mus musculus, were orally administered with different concentrations of aspartame (ASP; 7, 14, 28, and 35 mg/kg body weight), acesulfame-K (ASK; 150, 300, and 600 mg/kg body weight), and saccharin (50, 100, and 200 mg/kg body weight) individually. Concurrently negative and positive control sets were maintained. The animals were sacrificed and the bone marrow cells were processed for comet assay. The standard plate-incorporation assay was carried with the three sweeteners in Salmonella typhimurium TA 97a and TA 100 strains both in the absence and presence of the S9 mix. The comet parameters of DNA were increased in the bone marrow cells due to the sweetener-induced DNA strand breaks, as revealed by increased comet-tail extent and percent DNA in the tail. ASK and saccharin were found to induce greater DNA damage than ASP. However, none could act as a potential mutagen in the Ames/Salmonella /microsome test. These findings are important, since they represent a potential health risk associated with the exposure to these agents.

http://www.ncbi.nlm.nih.gov/pubmed/18850355

“Evidence indicates that a 12-wk administration of Splenda exerted numerous adverse effects, including (1) reduction in beneficial fecal microflora, (2) increased fecal pH, and (3) enhanced expression levels of P-gp, CYP3A4, and CYP2D1, which are known to limit the bioavailability of orally administered drugs.”

The Journal Of Toxicology And Environmental Health • Part A • December 2008

Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats

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Abstract

Splenda is comprised of the high-potency artificial sweetener sucralose (1.1%) and the fillers maltodextrin and glucose. Splenda was administered by oral gavage at 100, 300, 500, or 1000 mg/kg to male Sprague-Dawley rats for 12-wk, during which fecal samples were collected weekly for bacterial analysis and measurement of fecal pH. After 12-wk, half of the animals from each treatment group were sacrificed to determine the intestinal expression of the membrane efflux transporter P-glycoprotein (P-gp) and the cytochrome P-450 (CYP) metabolism system by Western blot. The remaining animals were allowed to recover for an additional 12-wk, and further assessments of fecal microflora, fecal pH, and expression of P-gp and CYP were determined. At the end of the 12-wk treatment period, the numbers of total anaerobes, bifidobacteria, lactobacilli, Bacteroides, clostridia, and total aerobic bacteria were significantly decreased; however, there was no significant treatment effect on enterobacteria. Splenda also increased fecal pH and enhanced the expression of P-gp by 2.43-fold, CYP3A4 by 2.51-fold, and CYP2D1 by 3.49-fold. Following the 12-wk recovery period, only the total anaerobes and bifidobacteria remained significantly depressed, whereas pH values, P-gp, and CYP3A4 and CYP2D1 remained elevated. These changes occurred at Splenda dosages that contained sucralose at 1.1-11 mg/kg (the US FDA Acceptable Daily Intake for sucralose is 5 mg/kg). Evidence indicates that a 12-wk administration of Splenda exerted numerous adverse effects, including (1) reduction in beneficial fecal microflora, (2) increased fecal pH, and (3) enhanced expression levels of P-gp, CYP3A4, and CYP2D1, which are known to limit the bioavailability of orally administered drugs.

http://www.ncbi.nlm.nih.gov/pubmed/18800291

International Journal Of Obesity (London) • December 2008

Sugary drinks in the pathogenesis of obesity and cardiovascular diseases

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Abstract

“Soft drink overconsumption is now considered to be a major public health concern with implications for cardiovascular diseases. This follows a number of studies performed in animals suggesting that chronic consumption of refined sugars can contribute to metabolic and cardiovascular dysregulation. In particular, the monosaccharide fructose has been attracting increasing attention as the more harmful sugar component in terms of weight gain and metabolic disturbances. High-fructose corn syrup is gradually replacing sucrose as the main sweetener in soft drinks and has been blamed as a potential contributor to the current high prevalence of obesity. There is also considerable evidence that fructose, rather than glucose, is the more damaging sugar component in terms of cardiovascular risk. This review focuses on the potential role of sugar drinks, particularly the fructose component, in the pathogenesis of obesity and cardiovascular diseases.”

http://www.ncbi.nlm.nih.gov/pubmed/19079277

“CONCLUSION:
Aspartame has a biological effect even at the recommended daily maximum dose.”

In Vivo • January 2007

The Effect of Aspartame Administration on Oncogene and Suppressor Gene Expressions

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Abstract

BACKGROUND:
Aspartame (L-phenylalanine N-L-alpha-aspartyl-1-methyl ester) is an artificial sweetener with widespread applications. Previously published results have shown that among rats receiving aspartame a significant increase of lymphoreticular neoplasms, brain tumours and transitional cell tumours occurred. The aim of our short-term experiment was to investigate the biological effect of aspartame consumption by determining the expressions of key oncogenes and a tumour suppressor gene.

MATERIALS AND METHODS:
After one week per os administration of various doses of aspartame to CBA/CA female mice, p53, c-myc, Ha-ras gene expression alterations were determined in individual organs.

RESULTS:
The results showed an increase in gene expressions concerning all the investigated genes especially in organs with a high proliferation rate: lymphoreticular organs, bone-marrow and kidney.

CONCLUSION:
Aspartame has a biological effect even at the recommended daily maximum dose.

Full Text PDF

http://iv.iiarjournals.org/content/21/1/89.long

The Journal Of The American Dietetic Association • June 2007

Regular sugar-sweetened beverage consumption between meals increases risk of overweight among preschool-aged children

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Abstract

OBJECTIVE

To examine the relationship between consumption of sugar-sweetened beverages (eg, nondiet carbonated drinks and fruit drinks) and the prevalence of overweight among preschool-aged children living in Canada.

DESIGN

Data come from the Longitudinal Study of Child Development in Québec (1998-2002).

SUBJECTS/SETTING

A representative sample (n=2,103) of children born in 1998 in Québec, Canada. A total of 1,944 children (still representative of the same-age children in this population) remaining at 4 to 5 years in 2002 participated in the nutrition study.

STATISTICAL ANALYSES PERFORMED

Data were collected via 24-hour dietary recall interview. Frequency of sugar-sweetened beverage consumption between meals at age 2.5, 3.5, and 4.5 years was recorded and children's height and weight were measured. Multivariate regression analysis was done with Statistical Analysis System software. Weighted data were adjusted for within-child variability and significance level was set at 5%.

RESULTS

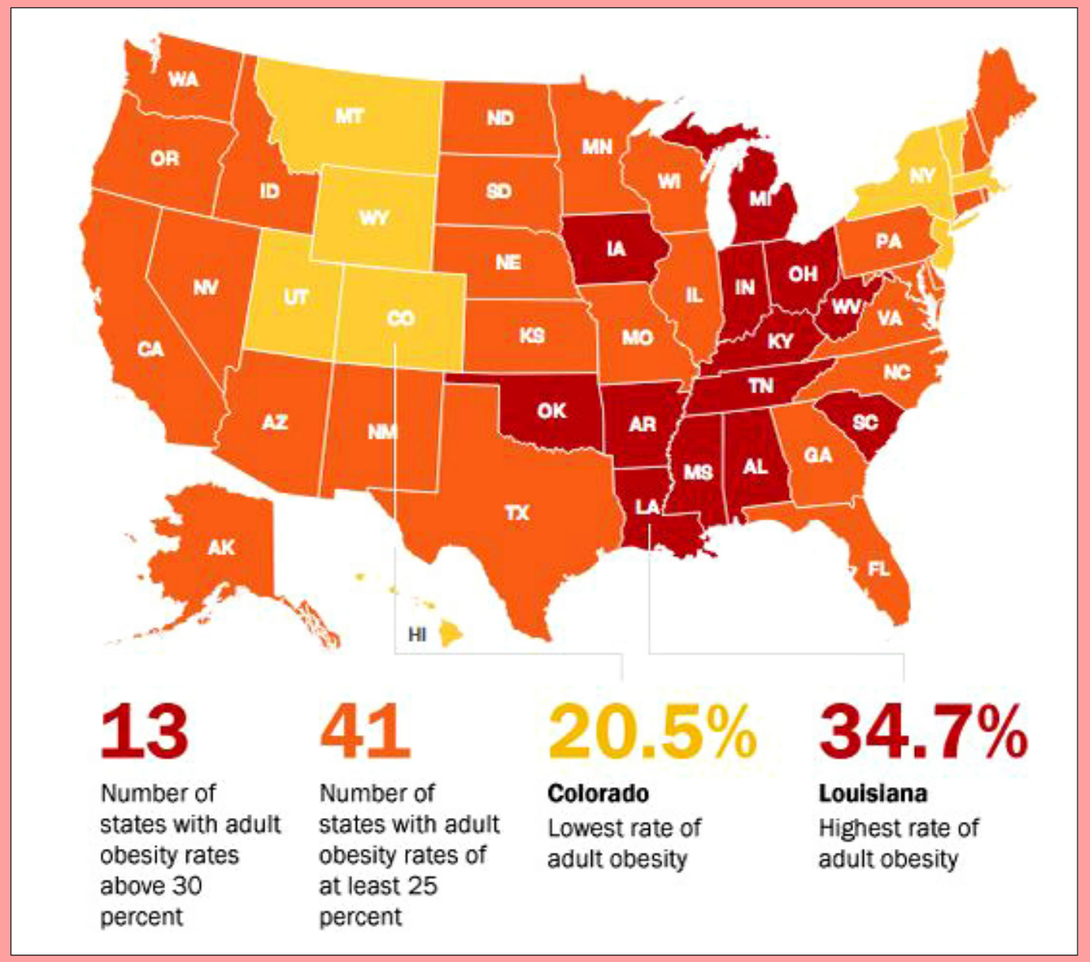
Overall, 6.9% of children who were nonconsumers of sugar-sweetened beverages between meals between the ages of 2.5 to 4.5 years were overweight at 4.5 years, compared to 15.4% of regular consumers (four to six times or more per week) at ages 2.5 years, 3.5 years, and 4.5 years. According to multivariate analysis, sugar-sweetened beverage consumption between meals more than doubles the odds of being overweight when other important factors are considered in multivariate analysis. Children from families with insufficient income who consume sugar-sweetened beverages regularly between the ages of 2.5 and 4.5 years are more than three times more likely to be overweight at age 4.5 years compared to nonconsuming children from sufficient income households.

CONCLUSIONS

Regular sugar-sweetened beverage consumption between meals may put some young children at a greater risk for overweight. Parents should limit the quantity of sweetened beverages consumed during preschool years because it may increase propensity to gain weight.

http://www.ncbi.nlm.nih.gov/pubmed/17524711

"Children from families with insufficient income who consume sugar-sweetened beverages regularly between the ages of 2.5 and 4.5 years are more than three times more likely to be overweight at age 4.5 years compared to non-consuming children from sufficient income households."



“... this carcinogenicity bioassay confirm and reinforce the first experimental demonstration of Aspartame’s multipotential carcinogenicity at a dose level close to the acceptable daily intake for humans.”

Environmental Health Perspectives • September 2007

Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effects in rats

Author information

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Abstract

BACKGROUND

In a previous study conducted at the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation (CMCRC/ERF), we demonstrated for the first time that aspartame (APM) is a multipotent carcinogenic agent when various doses are administered with feed to Sprague-Dawley rats from 8 weeks of age throughout the life span.

OBJECTIVE

The aim of this second study is to better quantify the carcinogenic risk of APM, beginning treatment during fetal life.

METHODS

We studied groups of 70-95 male and female Sprague-Dawley rats administered APM (2,000, 400, or 0 ppm) with feed from the 12th day of fetal life until natural death.

RESULTS

Our results show a) a significant dose-related increase of malignant tumor-bearing animals in males ($p < 0.01$), particularly in the group treated with 2,000 ppm APM ($p < 0.01$); b) a significant increase in incidence of lymphomas/leukemias in males treated with 2,000 ppm ($p < 0.05$) and a significant dose-related increase in incidence of lymphomas/leukemias in females ($p < 0.01$), particularly in the 2,000-ppm group ($p < 0.01$); and c) a significant dose-related increase in incidence of mammary cancer in females ($p < 0.05$), particularly in the 2,000-ppm group ($p < 0.05$).

CONCLUSIONS

The results of this carcinogenicity bioassay confirm and reinforce the first experimental demonstration of APM’s multipotential carcinogenicity at a dose level close to the acceptable daily intake for humans. Furthermore, the study demonstrates that when life-span exposure to APM begins during fetal life, its carcinogenic effects are increased.

Full text, graphs, charts and 32 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1964906/

“Aspartame compounds may directly and/or indirectly act on the frontal cortex acetylcholinesterase.”

Food Chemistry & Toxicology • December 2007

The effect of aspartame metabolites on the suckling rat frontal cortex acetylcholinesterase: An in vitro study

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Abstract

Aspartame (ASP) consumption is suggested to be implicated with muscarinic dysfunction. The aim of this work was to evaluate the effect of ASP and its metabolites on acetylcholinesterase (AChE) activity in rat frontal cortex and pure enzyme. Rat frontal cortex homogenate or pure enzyme AChE (eel E. Electricus) were incubated with ASP and each of ASP components, phenylalanine (Phe), aspartic acid (asp), and methanol (MeOH) for 1 h at 37 degrees C. AChE was measured spectrophotometrically. The results showed that incubation of rat tissue or pure enzyme with the sum of ASP metabolites, as reported to be found in the CSF after 150 or 200 mg/kg ASP consumption, inhibited frontal cortex and pure AChE about -11% to -29% ($p<0.001$). Asp, Phe or MeOH concentrations related to their CSF levels after ingestion of abuse or toxic ASP doses, when separately incubated with frontal cortex or pure AChE, resulted in a significant decrease of the enzyme activities.

IN CONCLUSION

ASP compounds may directly and/or indirectly act on the frontal cortex AChE. High or toxic doses of the sweetener remarkably decreased the enzyme activity. If this in vitro finding comes into human reality, it may be suggested that cholinergic [nerve cell] symptoms are related to the consumption of the above ASP doses.

http://www.ncbi.nlm.nih.gov/pubmed/17673349

“The results of this mega-experiment indicate that Aspartame is a multipotential carcinogenic agent, even at a daily dose of 20 mg/kg body weight, much less than the current acceptable daily intake. On the basis of these results, a reevaluation of the present guidelines on the use and consumption of Aspartame is urgent and cannot be delayed.”

Environmental Health Perspectives • March 2006

First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats

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Abstract

The Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation has conducted a long-term bioassay on aspartame (APM), a widely used artificial sweetener. APM was administered with feed to 8-week-old Sprague-Dawley rats (100-150/sex/group), at concentrations of 100,000, 50,000, 10,000, 2,000, 400, 80, or 0 ppm. The treatment lasted until natural death, at which time all deceased animals underwent complete necropsy. Histopathologic evaluation of all pathologic lesions and of all organs and tissues collected was routinely performed on each animal of all experimental groups. The results of the study show for the first time that APM, in our experimental conditions, causes a) an increased incidence of malignant-tumor-bearing animals with a positive significant trend in males ($p <$ or $= 0.05$) and in females ($p <$ or $= 0.01$), in particular those females treated at 50,000 ppm ($p <$ or $= 0.01$); b) an increase in lymphomas and leukemias with a positive significant trend in both males ($p <$ or $= 0.05$) and females ($p <$ or $= 0.01$), in particular in females treated at doses of 100,000 ($p <$ or $= 0.01$), 50,000 ($p <$ or $= 0.01$), 10,000 ($p <$ or $= 0.05$), 2,000 ($p <$ or $= 0.05$), or 400 ppm ($p <$ or $= 0.01$); c) a statistically significant increased incidence, with a positive significant trend ($p <$ or $= 0.01$), of transitional cell carcinomas of the renal pelvis and ureter and their precursors (dysplasias) in females treated at 100,000 ($p <$ or $= 0.01$), 50,000 ($p <$ or $= 0.01$), 10,000 ($p <$ or $= 0.01$), 2,000 ($p <$ or $= 0.05$), or 400 ppm ($p <$ or $= 0.05$); and d) an increased incidence of malignant schwannomas of peripheral nerves with a positive trend ($p <$ or $= 0.05$) in males. The results of this mega-experiment indicate that APM is a multipotential carcinogenic agent, even at a daily dose of 20 mg/kg body weight, much less than the current acceptable daily intake. On the basis of these results, a reevaluation of the present guidelines on the use and consumption of APM is urgent and cannot be delayed.

Full text, graphs, charts and 47 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1392232/

Understanding Synergy

Toxicology Science • March 2006

Synergistic interactions between commonly used food additives in a developmental neurotoxicity test

Author information
By K. Lau, WG. McLean, DP. Williams and CV. Howard

Abstract

Exposure to non-nutritional food additives during the critical development window has been implicated in the induction and severity of behavioral disorders such as attention deficit hyperactivity disorder (ADHD). Although the use of single food additives at their regulated concentrations is believed to be relatively safe in terms of neuronal development, their combined effects remain unclear. We therefore examined the neurotoxic effects of four common food additives in combinations of two (Brilliant Blue and L-glutamic acid, Quinoline Yellow and aspartame) to assess potential interactions. Mouse NB2a neuroblastoma cells were induced to differentiate and grow neurites in the presence of additives. After 24 h, cells were fixed and stained and neurite length measured by light microscopy with computerized image analysis. Neurotoxicity was measured as an inhibition of neurite outgrowth. Two independent models were used to analyze combination effects: effect additivity and dose additivity. Significant synergy was observed between combinations of Brilliant Blue with L-glutamic acid, and Quinoline Yellow with aspartame, in both models. Involvement of N-methyl-D-aspartate (NMDA) receptors in food additive-induced neurite inhibition was assessed with a NMDA antagonist, CNS-1102. L-glutamic acid- and aspartame-induced neurotoxicity was reduced in the presence of CNS-1102; however, the antagonist did not prevent food color-induced neurotoxicity. Theoretical exposure to additives was calculated based on analysis of content in foodstuff, and estimated percentage absorption from the gut. Inhibition of neurite outgrowth was found at concentrations of additives theoretically achievable in plasma by ingestion of a typical snack and drink. In addition, Trypan Blue dye exclusion was used to evaluate the cellular toxicity of food additives on cell viability of NB2a cells; both combinations had a straightforward additive effect on cytotoxicity. These data have implications for the cellular effects of common chemical entities ingested individually and in combination.

Full text, graphs, charts and 45 references

http://toxsci.oxfordjournals.org/content/90/1/178.full.pdf+html

Headache • March 2006

Migraine triggered by sucralose—a case report

Author information

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Abstract

Sucralose is the active compound of the most commonly sold sweetener in the United States. Different than aspartame, sucralose is not considered to be a migraine trigger. Herein we report a patient with attacks of migraine consistently triggered by sucralose. She also suffers from menstrually related migraine that had been well-controlled for several months since she switched her contraceptive from fixed estrogen to triphasic contraceptive pills. Some attacks triggered by sucralose were preceded by aura, and she had never experienced migraine with aura before. Withdrawal of the compound was associated with complete resolution of the attacks. Single-blind exposure (vs. sugar) triggered the attacks, after an attack-free period.

http://www.ncbi.nlm.nih.gov/pubmed/16618274

“Consumption of sugar-sweetened beverages (SSBs), particularly carbonated soft drinks, may be a key contributor to the epidemic of overweight and obesity, by virtue of these beverages’ high added sugar content, low satiety, and incomplete compensation for total energy. The weight of epidemiologic and experimental evidence indicates that a greater consumption of Sugar-Sweetened Beverages is associated with weight gain and obesity.”

American Journal Of Clinical Nutrition • August 2006

Intake of sugar-sweetened beverages and weight gain: a systematic review

Author information

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Abstract

Consumption of sugar-sweetened beverages (SSBs), particularly carbonated soft drinks, may be a key contributor to the epidemic of overweight and obesity, by virtue of these beverages’ high added sugar content, low satiety, and incomplete compensation for total energy. Whether an association exists between SSB intake and weight gain is unclear. We searched English-language MEDLINE publications from 1966 through May 2005 for cross-sectional, prospective cohort, and experimental studies of the relation between SSBs and the risk of weight gain (ie, overweight, obesity, or both). Thirty publications (15 cross-sectional, 10 prospective, and 5 experimental) were selected on the basis of relevance and quality of design and methods. Findings from large cross-sectional studies, in conjunction with those from well-powered prospective cohort studies with long periods of follow-up, show a positive association between greater intakes of SSBs and weight gain and obesity in both children and adults. Findings from short-term feeding trials in adults also support an induction of positive energy balance and weight gain by intake of sugar-sweetened sodas, but these trials are few. A school-based intervention found significantly less soft-drink consumption and prevalence of obese and overweight children in the intervention group than in control subjects after 12 mo, and a recent 25-week randomized controlled trial in adolescents found further evidence linking SSB intake to body weight. The weight of epidemiologic and experimental evidence indicates that a greater consumption of SSBs is associated with weight gain and obesity. Although more research is needed, sufficient evidence exists for public health strategies to discourage consumption of sugary drinks as part of a healthy lifestyle.

Full text, graphs, charts and 113 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3210834/

Environmental Health Perspective • September 2006

Testing Needed for Acesulfame Potassium, an Artificial Sweetener

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The author declares that she has no competing financial interests. See the reply "Acesulfame Potassium: Soffritti Responds" on page A516
See the article "First Experimental Demonstration of the Multipotential Carcinogenic Effects of Aspartame Administered in the Feed to Sprague-Dawley Rats" in volume 114 on page 379.
This article has been cited by other articles in PMC.

Abstract

In their article "First Experimental Demonstration of the Multipotential Carcinogenic Effects of Aspartame Administered in the Feed of Sprague-Dawley Rats," Soffritti et al. (2006) present interesting data on the carcinogenic effects of long-term exposure to aspartame, an artificial sweetener, in experimental animals (rats). Recently, aspartame was supplanted as the leading artificial sweetener by sucralose, marketed in the United States under the trade name Splenda (McNeil Nutritionals, LLC, Ft. Washington, PA). As of 2005, Splenda was reported to have > 50% of the market for artificial sweeteners, while aspartame [Equal (Merisant Company, Chicago, IL); NutraSweet (NutraSweet Property Holdings Inc., Chicago, IL)] had < 20% (Associated Press 2005). Splenda is typically used in sweetener blends, most frequently with acesulfame potassium (CAS RN 55589-62-3) (Sunett; marketed in the United States by Nutrinova, Somerset, NJ).

The Food and Drug Administration's (FDA) multiple approvals of food additive petitions (FAPs) for acesulfame began in 1988 (FDA 1988), and culminated in 1998 with approval of the use of acesulfame in soft drinks (FDA 1998), historically the largest single use of artificial sweeteners. All of the FDA's approvals of FAPs for acesulfame were grounded on the conclusion that safety studies, including long-term animal tests of acesulfame carried out for Hoechst, the manufacturer of the chemical, in the Netherlands in the 1970s, were adequate and the test results indicated safety.

The 1970s tests of acesulfame—two tests carried out in rats and one in mice—are inadequate to establish lack of potential carcinogenicity. Here are a few reasons why the tests are inadequate [Center for Science in the Public Interest (CSPI) 1996]:

- Subchronic tests were not conducted for the rats and mice used in the tests on which the FAPs rested
- It is likely the minimum toxic dose/maximum tolerated dose (MTD) was not achieved in the rat and mouse studies
- Randomization of test groups was not carried out properly
- Mice were held on test for only 80 weeks, rather than the 104 weeks characteristic of National Toxicology Program (NTP) bioassays

• Animal husbandry and monitoring of animals on test were evidently poor, as indicated by high disease rates in the animals and extensive autolysis of tissues.

Even with the flaws in design and execution of the Hoechst tests, results indicated an association between treatment with acesulfame and carcinogenesis (CSPI 1996). The question remains whether these studies are sufficiently definitive or rigorous in light of the potential for widespread, [sic] high exposure to acesulfame K in all group [sic] in the population.

In 1996, the CSPI nominated acesulfame for testing in the NTP bioassay program (CSPI 1996), and provided the NTP with detailed information on the Hoechst tests and their flaws. Although an individual familiar with test design and implementation could have concluded with ease that the Hoechst tests were not consistent with the criteria established for NTP bioassays or the test guidelines set out in the FDA's Redbook (FDA 1982), and that it was likely that, at some point, many people would be exposed to acesulfame, the NTP rejected CSPI's nomination.

In 2003, the NTP announced the results of tests of both aspartame and acesulfame in genetically modified mice (GMM) (NTP 2005). Both chemicals gave negative results in the tests, carried out in two strains of GMM. The NTP's final report on those GMM studies (NTP 2005) noted that aspartame and acesulfame had been selected as "negative controls" for validation tests for the GMM models. The chemicals did indeed test negative, but that negative result did not advance our understanding of potential carcinogenicity of acesulfame. Regarding the GMM tests of aspartame and acesulfame, Martha Sandy of the California Environmental Protection Agency, stated that:

"[N]egative results [in the GMM tests] are not informative as to the test substance's carcinogenicity, and point to the need to conduct standard two-year carcinogenicity studies. At this time, transgenic models cannot replace the two-year bioassay and it would be unwise to list a chemical as safe for human exposure based upon negative results in not yet validated model systems."

(Sandy 2003) The findings of Soffritti et al. (2006) of multipotential carcinogenesis in rats fed aspartame over their lifetimes provide support for Sandy's (2003) statements. I have sent the NTP a new nomination of acesulfame for 2-year bioassay testing (Karstadt 2006). Full Text with References:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1570055/

“This observation of a potential causal relationship between sucralose and migraines may be important for physicians to remember ...”

Headache • September 2006

Popular sweetener sucralose as a migraine trigger

Author information

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Abstract

Sucralose (trichlorogalactosucrose, or better known as Splenda) is an artificial sweetener from native sucrose that was approved by the FDA on April 1, 1998 (April Fool’s Day). This observation of a potential causal relationship between sucralose and migraines may be important for physicians to remember this can be a possible trigger during dietary history taking. Identifying further triggers for migraine headaches, in this case sucralose, may help alleviate some of the cost burden (through expensive medical therapy or missed work opportunity) as well as provide relief to migraineurs.

http://www.ncbi.nlm.nih.gov/pubmed/16942478

“The results of this mega-experiment indicate that Aspartame, in the tested experimental conditions, is a multipotential carcinogenic agent.”

Annals Of The New York Academy Of Sciences • September 2006

Results of long-term carcinogenicity bioassay on Sprague-Dawley rats exposed to aspartame administered in feed

Author information

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Abstract

Aspartame (APM) is one of the most widely used artificial sweeteners in the world. Its ever-growing use in more than 6000 products, such as soft drinks, chewing gum, candy, desserts, etc., has been accompanied by rising consumer concerns regarding its safety, in particular its potential long-term carcinogenic effects. In light of the inadequacy of the carcinogenicity bioassays performed in the 1970s and 1980s, a long-term mega-experiment on APM was undertaken at the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation on groups of male and female Sprague-Dawley rats (100-150/sex/group), 8 weeks old at the start of the experiment. APM was administered in feed at concentrations of 100,000, 50,000, 10,000, 2,000, 400, 80, or 0 ppm. Treatment lasted until spontaneous death of the animals. The results of the study demonstrate that APM causes: (a) an increased incidence of malignant tumor-bearing animals, with a positive significant trend in both sexes, and in particular in females treated at 50,000 ppm (P < or = 0.01) when compared to controls; (b) an increase in lymphomas-leukemias, with a positive significant trend in both sexes, and in particular in females treated at doses of 100,000 (P < or = 0.01), 50,000 (P < or = 0.01), 10,000 (P < or = 0.05), 2000 (P < or = 0.05), and 400 ppm (P < or = 0.01); (c) a statistically significant increased incidence, with a positive significant trend, of transitional cell carcinomas of the renal pelvis and ureter in females and particularly in those treated at 100,000 ppm (P < or = 0.05); and (d) an increased incidence of malignant schwannomas of the peripheral nerves, with a positive trend in males (P < or = 0.05). The results of this mega-experiment indicate that APM, in the tested experimental conditions, is a multipotential carcinogenic agent.

http://www.ncbi.nlm.nih.gov/pubmed/17119233

Journal Of Dental Research • October 2006

The role of sucrose in cariogenic dental biofilm formation—new insight

Author information

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Abstract

Dental caries is a biofilm-dependent oral disease, and fermentable dietary carbohydrates are the key environmental factors involved in its initiation and development. However, among the carbohydrates, sucrose is considered the most cariogenic, because, in addition to being fermented by oral bacteria, it is a substrate for the synthesis of extracellular (EPS) and intracellular (IPS) polysaccharides. Therefore, while the low pH environment triggers the shift of the resident plaque microflora to a more cariogenic one, EPS promote changes in the composition of the biofilms' matrix. Furthermore, it has recently been shown that the biofilm formed in the presence of sucrose presents low concentrations of Ca, P(i), and F, which are critical ions involved in de- and remineralization of enamel and dentin in the oral environment. Thus, the aim of this review is to explore the broad role of sucrose in the cariogenicity of biofilms, and to present a new insight into its influence on the pathogenesis of dental caries.

Full text, graphs, charts and 90 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2257872/

DENTAL CARIES

Dental caries, also known as tooth decay, cavities, or caries, is a breakdown of teeth due to the activities of bacteria. The cavities may be a number of different colors from yellow to black. Symptoms may include pain and difficulty with eating. Complications may include inflammation of the tissue around the tooth, tooth loss, and infection or abscess formation.

The cause of caries is bacterial breakdown of the hard tissues of the teeth (enamel, dentin and cementum). This occurs due to acid made from food debris or sugar on the tooth surface. Simple sugars in food are these bacteria's primary energy source and thus a diet high in simple sugar is a risk factor. If mineral breakdown is greater than build up from sources such as saliva, caries results. Risk factors include conditions that result in less saliva such as: diabetes mellitus, Sjogren's syndrome and some medications. Medications that decrease saliva production include antihistamines, antidepressants and cannabis among others. Caries is also associated with poverty, poor cleaning of the mouth, and receding gums resulting in exposure of the roots of the teeth.

Prevention includes: regular cleaning of the teeth and a diet low in sugar. Brushing the teeth two times per day and flossing between the teeth once a day is recommended by most doctors. Treating a mother's dental caries may decrease the risk in her children by decreasing the numbers of certain bacteria. Screening can result in earlier detection. Depending on the extent of destruction, various treatments can be used to restore the tooth to proper function or the tooth may be removed. The availability of treatment is often poor in the developing world.

Worldwide, approximately 2.43 billion people (36% of the population) have dental caries in their permanent teeth. The World Health Organizations estimates that nearly all adults have dental caries at some point in time. In baby teeth it affects about 620 million people or 9% of the population. They have become more common in both children and adults in recent years with the extraordinary increase in the use of sugar and sugar-like artificial substitutes. The disease is most common in the developed world and less common in the developing world due to greater simple sugar consumption. By the way, caries is Latin for "rottenness".

“During the intervention, sucrose intake increased by 151% in the sucrose group and decreased by 42% in the sweetener group, resulting in a 1.6-kg weight gain in the sucrose group and a 1.2-kg weight loss in the sweetener group over 10 wk ...”

American Journal Of Clinical Nutrition • August 2005

Effect of sucrose on inflammatory markers in overweight humans

Author information

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Abstract

BACKGROUND

Observational studies have found that dietary glycemic load is positively associated with C-reactive protein (CRP) concentrations in healthy humans, which suggests that the type of carbohydrate ingested influences inflammatory activity.

OBJECTIVE

We investigated the effect of a diet with a high content of sucrose or artificial sweeteners on the inflammatory markers CRP, haptoglobin, and transferrin in overweight subjects.

DESIGN

Overweight men and women consumed daily food and drink supplements containing either sucrose [n = 21; body mass index (BMI, in kg/m2): 28.0] or artificial sweeteners (n = 20; BMI: 27.6), predominantly from soft drinks (70%; average approximately 1.3 L/d) for 10 wk.

RESULTS

During the intervention, sucrose intake increased by 151% in the sucrose group and decreased by 42% in the sweetener group, resulting in a 1.6-kg weight gain in the sucrose group and a 1.2-kg weight loss in the sweetener group over 10 wk ($P < 0.001$). Concentrations of haptoglobin, transferrin, and CRP increased by 13%, 5%, and 6%, respectively, in the sucrose group and decreased by 16%, 2%, and 26%, respectively, in the sweetener group (between-group differences: $P = 0.006$, $P = 0.01$, and $P = 0.1$, respectively). Adjustment for changes in body weight and energy intake did not substantially influence this outcome.

CONCLUSIONS

The study shows that in the present group of overweight subjects a high consumption of sugar-sweetened foods and drinks increased haptoglobin and transferrin but had, at best, only a limited influence on CRP.

Full text with 28 references

http://ajcn.nutrition.org/content/82/2/421.long

“Glyoxal is capable of inducing cellular damage, like methylglyoxal (MG), but may also accelerate the rate of glycation leading to the formation of advanced glycation end-products (AGEs).”

Biochemistry And Pharmacology • October 2004

The cytotoxic mechanism of glyoxal involves oxidative stress

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Abstract

Glyoxal is a reactive alpha-oxoaldehyde that is a physiological metabolite formed by lipid peroxidation, ascorbate autoxidation, oxidative degradation of glucose and degradation of glycated proteins. Glyoxal is capable of inducing cellular damage, like methylglyoxal (MG), but may also accelerate the rate of glycation leading to the formation of advanced glycation end-products (AGEs). However, the mechanism of glyoxal cytotoxicity has not been precisely defined. In this study we have focused on the cytotoxic effects of glyoxal and its ability to overcome cellular resistance to oxidative stress. Isolated rat hepatocytes were incubated with different concentrations of glyoxal. Glyoxal by itself was cytotoxic at 5mM, depleted GSH, formed reactive oxygen species (ROS) and collapsed the mitochondrial membrane potential. Glyoxal also induced lipid peroxidation and formaldehyde formation. Glycolytic substrates, e.g. fructose, sorbitol and xylitol inhibited glyoxal-induced cytotoxicity and prevented the decrease in mitochondrial membrane potential suggesting that mitochondrial toxicity contributed to the cytotoxic mechanism. Glyoxal cytotoxicity was prevented by the glyoxal traps d-penicillamine or aminoguanidine or ROS scavengers were also cytoprotective even when added some time after glyoxal suggesting that oxidative stress contributed to the glyoxal cytotoxic mechanism.

http://www.ncbi.nlm.nih.gov/pubmed/15345333

GLYOXAL

Glyoxal is an organic compound with the formula OCHCHO. It is a yellow-colored liquid that evaporates to give a green-colored gas. Glyoxal is the smallest dialdehyde (two aldehyde groups). Its structure is more complicated than typically represented because the molecule hydrates and oligomerizes. It is produced industrially as a precursor to many products.

Coated paper and textile finishes use large amounts of glyoxal as a crosslinker for starch-based formulations. It condenses with urea to afford 4,5-dihydroxy-2-imidazolidinone, which further reacts with formaldehyde to give the bis(hydroxymethyl) derivative used for wrinkle-resistant chemical treatments. It is used as a solubilizer and cross-linking agent in polymer chemistry:

- proteins (leather tanning process)
- collagen
- cellulose derivatives (textiles)
- hydrocolloids
- starch (paper coatings)

Glyoxal is a valuable building block in organic synthesis, especially in the synthesis of heterocycles such as imidazoles. A convenient form of the reagent for use in the laboratory is its bis-hemiacetal with ethylene glycol, 1,4-dioxane-2,3-diol. This compound is commercially available. Glyoxal solutions can also be used as a fixative for histology, that is, a method of preserving cells for examining them under a microscope.

Glyoxal In Food And The Environment

Glyoxal is an inflammatory compound formed when cooking oils and fats are heated to high temperatures. Glyoxal has been observed as a trace-gas in the atmosphere, e.g. as an oxidation product of hydrocarbons. Tropospheric concentrations of 0-200 pptv have been reported, in polluted regions up to 1 ppbv.

“Higher consumption of sugar-sweetened beverages is associated with a greater magnitude of weight gain and an increased risk for development of type 2 diabetes in women ...”

Journal Of The American Medical Association JAMA • August 2004

Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women

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Abstract

CONTEXT

Sugar-sweetened beverages like soft drinks and fruit punches contain large amounts of readily absorbable sugars and may contribute to weight gain and an increased risk of type 2 diabetes, but these relationships have been minimally addressed in adults.

OBJECTIVE

To examine the association between consumption of sugar-sweetened beverages and weight change and risk of type 2 diabetes in women.

DESIGN, SETTING, AND PARTICIPANTS

Prospective cohort analyses conducted from 1991 to 1999 among women in the Nurses' Health Study II. The diabetes analysis included 91,249 women free of diabetes and other major chronic diseases at baseline in 1991. The weight change analysis included 51,603 women for whom complete dietary information and body weight were ascertained in 1991, 1995, and 1999. We identified 741 incident cases of confirmed type 2 diabetes during 716,300 person-years of follow-up.

MAIN OUTCOME MEASURES

Weight gain and incidence of type 2 diabetes.

RESULTS

Those with stable consumption patterns had no difference in weight gain, but weight gain over a 4-year period was highest among women who increased their sugar-sweetened soft drink consumption from 1 or fewer drinks per week to 1 or more drinks per day (multivariate-adjusted means, 4.69 kg for 1991 to 1995 and 4.20 kg for 1995 to 1999) and was smallest among women who decreased their intake (1.34 and 0.15 kg for the 2 periods, respectively) after adjusting for lifestyle and dietary confounders. Increased consumption of fruit punch was also associated with greater weight gain compared with decreased consumption. After adjustment for potential confounders, women consuming 1 or more sugar-sweetened soft drinks per day had a relative risk [RR] of type 2 diabetes of 1.83 (95% confidence interval [CI], 1.42-2.36; P<.001 for trend) compared with those who consumed less than 1 of these beverages per month. Similarly, consumption of fruit punch was associated with increased diabetes risk (RR for > or =1 drink per day compared with <1 drink per month, 2.00; 95% CI, 1.33-3.03; P =.001).

CONCLUSION

Higher consumption of sugar-sweetened beverages is associated with a greater magnitude of weight gain and an increased risk for development of type 2 diabetes in women, possibly by providing excessive calories and large amounts of rapidly absorbable sugars.

http://www.ncbi.nlm.nih.gov/pubmed/15328324/

Biochemical Society Transactions • December 2003

Toxicity of Glyoxals—
role of oxidative stress, metabolic detoxification and thiamine deficiency

Author information

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Abstract

Glyoxals are reactive alpha-oxoaldehydes that are formed endogenously from sugars, the levels of which are increased in various pathological conditions associated with hyperglycaemia and thiamine deficiency. However, the molecular cytotoxic mechanisms of glyoxal are not known. Results presented here and in the other studies cited provide a glimpse into the cytotoxicity mechanisms involved and their pathological implications. We found that glyoxal (10 microM) markedly increased the susceptibility of hepatocyte glutathione (GSH) to oxidation by hydrogen peroxide (H(2)O(2)) and markedly increased cytotoxicity by compromising the cellular antioxidant enzyme system. At higher concentrations, glyoxal was cytotoxic towards hepatocytes, which can be attributed to GSH depletion, oxidative stress and mitochondrial toxicity. Aminoguanidine or penicillamine protected the hepatocytes. Glyoxal cytotoxicity was prevented by increasing glyoxal metabolism with thiamine or NAD(P)H generators, and was increased in GSH- or thiamine-deficient hepatocytes. It was also found that feeding rats reduced thiamine levels in a diet high in simple sugars increased the number of aberrant crypt foci/colon in the absence of clinical evidence of beriberi. This was associated with decreased plasma thiamine and low erythrocyte transketolase activity. Western diets, which are frequently poor in thiamine and high in sugars, could result in increased levels of endogenous glyoxals, which in turn may lead to a predisposition to AGE (advanced glycation end-product)-related pathologies and neoplastic conditions.

http://www.ncbi.nlm.nih.gov/pubmed/14641070

“Of all the additives, dyes were the most genotoxic. Amaranth, Allura Red, New Coccine, Tartrazine, Erythrosine, Phloxine, and Rose Bengal induced dose-related DNA damage in the glandular stomach, colon, and/or urinary bladder. All seven dyes induced DNA damage in the gastrointestinal organs at a low dose (10 or 100mg/kg). Among them, Amaranth, Allura Red, New Coccine, and Tartrazine induced DNA damage in the colon at close to the acceptable daily intakes (ADIs). Two antioxidants (butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)), three fungicides (biphenyl, sodium o-phenylphenol, and thiabendazole), and four sweeteners (sodium cyclamate, saccharin, sodium saccharin, and sucralose) also induced DNA damage in gastrointestinal organs.”

Mutation Research • August 2002

The comet assay with 8 mouse organs: results with 39 currently used food additives

Author information

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Abstract

We determined the genotoxicity of 39 chemicals currently in use as food additives. They fell into six categories-dyes, color fixatives and preservatives, preservatives, antioxidants, fungicides, and sweeteners. We tested groups of four male ddY mice once orally with each additive at up to 0.5xLD(50) or the limit dose (2000mg/kg) and performed the comet assay on the glandular stomach, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow 3 and 24h after treatment. Of all the additives, dyes were the most genotoxic. Amaranth, Allura Red, New Coccine, Tartrazine, Erythrosine, Phloxine, and Rose Bengal induced dose-related DNA damage in the glandular stomach, colon, and/or urinary bladder. All seven dyes induced DNA damage in the gastrointestinal organs at a low dose (10 or 100mg/kg). Among them, Amaranth, Allura Red, New Coccine, and Tartrazine induced DNA damage in the colon at close to the acceptable daily intakes (ADIs). Two antioxidants (butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)), three fungicides (biphenyl, sodium o-phenylphenol, and thiabendazole), and four sweeteners (sodium cyclamate, saccharin, sodium saccharin, and sucralose) also induced DNA damage in gastrointestinal organs. Based on these results, we believe that more extensive assessment of food additives in current use is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/12160896

“I also provide evidence to suggest that saccharin could be the causative or one of the most important risk factors for inflammatory bowel disease as for its inhibition on beta-glucuronidase in the intestine.”

Medical Hypotheses • August 2002

Impaired inactivation of digestive proteases by deconjugated bilirubin: the possible mechanism for inflammatory bowel disease

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Abstract

Inflammatory bowel disease refers to ulcerative colitis and Crohn’s disease, two gut diseases with unknown causes. The dramatic increase in the last half century and the big difference in incidence for people with the same ethnic background but living in different areas strongly suggested that environmental factors played the dominant role for these diseases. The similarity in many aspects for these two diseases suggested a common causative factor. Here I suggest the impaired inactivation of digestive proteases by deconjugated bilirubin, as the result of the inhibition of bilirubin deconjugation enzyme, beta-glucuronidase, originated from the luminal bacteria and mucosa of the gut, to be a possible mechanism for both ulcerative colitis and Crohn’s diseases. I also provide evidence to suggest that saccharin could be the causative or one of the most important risk factors for inflammatory bowel disease as for its inhibition on beta-glucuronidase in the intestine.

http://www.ncbi.nlm.nih.gov/pubmed/12208202

“Any evidence of carcinogenesis—and there is ample such evidence—of such a widely used chemical should spur health officials to minimize human exposure to it.”

International Journal Of Occupational Environmental Health • October 2002

Carcinogenicity of saccharin in laboratory animals and humans: Letter to Dr. Harry Conacher of Health Canada

Author information

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Abstract

We appreciate this opportunity to provide input to the Health Protection Branch’s (HPB’s) review of the artificial sweetener saccharin. Concerns with regard to the safety of saccharin are of great public health significance and of great interest to the public because saccharin is consumed by tens of millions of people, including children and fetuses. Any evidence of carcinogenesis—and there is ample such evidence—of such a widely used chemical should spur health officials to minimize human exposure to it. It is worth noting that on October 31, 1997, the Board of Scientific Counselors of the National Toxicology Program, a unit of the National Institute of Environmental Health Sciences (NIEHS), voted not to delist saccharin from its Report on Carcinogens.

http://www.ncbi.nlm.nih.gov/pubmed/12412858

“Overweight subjects who consumed fairly large amounts of sucrose (28% of energy), mostly as beverages, had increased energy intake, body weight, fat mass, and blood pressure after 10 wk.”

American Journal Of Clinical Nutrition • October 2002

Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects

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Abstract

BACKGROUND

The role of artificial sweeteners in body-weight regulation is still unclear.

OBJECTIVE

We investigated the effect of long-term supplementation with drinks and foods containing either sucrose or artificial sweeteners on ad libitum food intake and body weight in overweight subjects.

DESIGN

For 10 wk, overweight men and women consumed daily supplements of either sucrose [n = 21, body mass index (BMI; in kg/m(2)) = 28.0] or artificial sweeteners (n = 20, BMI = 27.6). On average, sucrose supplements provided 3.4 MJ and 152 g sucrose/d and sweetener supplements provided 1.0 MJ and 0 g sucrose/d.

RESULTS

After 10 wk, the sucrose group had increases in total energy (by 1.6 MJ/d), sucrose (to 28% of energy), and carbohydrate intakes and decreases in fat and protein intakes. The sweetener group had small but significant decreases in sucrose intake and energy density. Body weight and fat mass increased in the sucrose group (by 1.6 and 1.3 kg, respectively) and decreased in the sweetener group (by 1.0 and 0.3 kg, respectively); the between-group differences were significant at $P < 0.001$ (body weight) and $P < 0.01$ (fat mass). Systolic and diastolic blood pressure increased in the sucrose group (by 3.8 and 4.1 mm Hg, respectively) and decreased in the sweetener group (by 3.1 and 1.2 mm Hg, respectively).

CONCLUSIONS

Overweight subjects who consumed fairly large amounts of sucrose (28% of energy), mostly as beverages, had increased energy intake, body weight, fat mass, and blood pressure after 10 wk. These effects were not observed in a similar group of subjects who consumed artificial sweeteners.

Full text with 46 references

http://ajcn.nutrition.org/content/76/4/721.long

“Intakes of added sweeteners exceed levels compatible with meeting current dietary recommendations.”

Journal Of The American Dietetic Association • January 2000

Food sources of added sweeteners in the diets of Americans

By J.F. Guthrie[1] and J.F. Morton
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Abstract

OBJECTIVE
To identify food sources of added sweeteners in the US diet.

DESIGN
A descriptive study using data from the US Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals. Each subject provided one 24-hour dietary recall. Intake of added sweeteners was calculated using the USDA Food Guide Pyramid servings database.

SUBJECTS/SETTING
A national sample of noninstitutionalized persons aged 2 years and older (N = 15,010).

STATISTICAL ANALYSES
Mean intakes of added sweeteners from all food sources and from specific food categories; percentage contribution of added sweeteners to total energy intake; and percentage contribution of each food category to total intake of added sweeteners. All analyses were conducted for the total sample and for 12 age-gender groups.

RESULTS
During 1994 to 1996, Americans aged 2 years and older consumed the equivalent of 82 g carbohydrate per day from added sweeteners, which accounted for 16% of total energy intake. In absolute terms, adolescent males consumed the most; as a percentage of energy, male and female adolescents had the highest intakes (averaging 20% of total energy from added sweeteners). The largest source of added sweeteners was regular soft drinks, which accounted for one third of intake. Other sources were table sugars, syrups, and sweets; sweetened grains; regular fruitades/drinks; and milk products.

APPLICATIONS/CONCLUSIONS
Intakes of added sweeteners exceed levels compatible with meeting current dietary recommendations. Knowing food sources of added sweeteners for the overall population and for specific age-gender groups can help dietitians provide appropriate nutrition education.

http://www.ncbi.nlm.nih.gov/pubmed/10646004

Food Chemistry And Toxicology • December 2000

A combined chronic toxicity/carcinogenicity study of sucralose in Sprague-Dawley rats

Author information

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Abstract

The chronic toxicity and potential carcinogenicity of sucralose was evaluated by exposing Sprague-Dawley rats to dietary concentrations of this low-calorie sweetener both in utero and for up to 104 weeks following parturition. The rats assigned to the toxicity phase of this investigation were administered diets containing either 0% (control), 0.3% (3000 ppm), 1.0% (10,000 ppm) or 3.0% (30,000 ppm) sucralose. Each treatment group comprised 30 male and 30 female rats, of which 15 males and 15 females were sacrificed after 52 weeks of treatment. The surviving rats were killed following 78 weeks of sucralose administration. In the carcinogenicity phase of this investigation, groups of 50 male and 50 female rats were administered dietary sucralose at concentrations of 0% (control 1), 0% (control 2), 0.3%, 1.0% or 3.0% for 104 weeks. Evaluation of the data obtained from the two phases of this study showed that sucralose was not carcinogenic. Sucralose did not adversely affect the survival or clinical condition of the rats, and there were no toxicologically significant findings. Group mean body weight gain and food consumption were significantly decreased in a dose-dependent manner in sucralose-treated rats throughout the treatment period as compared to the controls. The primary effect of sucralose on food consumption, and secondarily on body weight gain, was established in later studies to be due to the fact that diets containing high concentrations of sucralose are unpalatable to rats. These subsequent studies established that the reduction of body weight gain seen in previous rat studies using sucralose in the diet at concentrations of 1% and below resulted from reduced food intake as a direct consequence of the unpalatable nature of sucralose. Similarly, at concentrations of 3% in the diet, it was shown that approximately 95% of the effect on body weight gain could be attributed to the reduction in food intake due to the reduced palatability of the diet, the remainder apparently due to a physiologic response to the high concentrations of non-digestible sucralose in the rats' diet. Complete toxicological evaluations of gavage studies with histopathological evaluations demonstrated that even at the 3% dietary level, toxicity was not responsible for the small body weight gain decrement. Gross and histopathologic examinations revealed that the administration of sucralose affected neither the types nor incidence of the tumours observed. The incidences of some non-neoplastic findings were statistically significantly increased in the sucralose treated groups relative to the controls. These included: renal pelvic epithelial hyperplasia in all female treatment groups, renal pelvic mineralization in females administered the intermediate or highest dietary concentrations of sucralose, adrenal cortical haemorrhagic degeneration in high-dose group female rats, and the histopathologic incidence of cataracts at necropsy in high-dose group male rats. The non-neoplastic findings that occurred were of no toxicological significance since they were either spontaneous findings commonly observed in aged rats of this strain or the physiological response to high dietary levels of a poorly absorbed compound.

http://www.ncbi.nlm.nih.gov/pubmed/10882819

"The incidences of some non-neoplastic findings were statistically significantly increased in the sucralose treated groups relative to the controls.

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at necropsy in high-dose group male rats."

“The rapid absorption of glucose after consumption of high-dietary glycemic index meals induces a sequence of hormonal and metabolic changes that promote excessive food intake in obese subjects.”

Pediatrics • March 1999

High glycemic index foods, overeating, and obesity

Author information

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Abstract

OBJECTIVE

The prevalence of obesity has increased dramatically in recent years. However, the role of dietary composition in body weight regulation remains unclear. The purpose of this work was to investigate the acute effects of dietary glycemic index (GI) on energy metabolism and voluntary food intake in obese subjects.

METHODS

Twelve obese teenage boys were evaluated on three separate occasions using a crossover study protocol. During each evaluation, subjects consumed identical test meals at breakfast and lunch that had a low, medium, or high GI. The high- and medium-GI meals were designed to have similar macronutrient composition, fiber content, and palatability, and all meals for each subject had equal energy content. After breakfast, plasma and serum concentrations of metabolic fuels and hormones were measured. Ad libitum food intake was determined in the 5-hour period after lunch.

RESULTS

Voluntary energy intake after the high-GI meal (5.8 megajoule [mJ]) was 53% greater than after the medium-GI meal (3.8 mJ), and 81% greater than after the low-GI meal (3.2 mJ). In addition, compared with the low-GI meal, the high-GI meal resulted in higher serum insulin levels, lower plasma glucagon levels, lower postabsorptive plasma glucose and serum fatty acids levels, and elevation in plasma epinephrine. The area under the glycemic response curve for each test meal accounted for 53% of the variance in food intake within subjects.

CONCLUSIONS

The rapid absorption of glucose after consumption of high-GI meals induces a sequence of hormonal and metabolic changes that promote excessive food intake in obese subjects. Additional studies are needed to examine the relationship between dietary GI and long-term body weight regulation.

http://www.ncbi.nlm.nih.gov/pubmed/10049982

“It is concluded that aspartame consumption may constitute a hazard because of its contribution to the formation of formaldehyde adducts.”

Life Sciences • January 1998

Formaldehyde derived from dietary aspartame binds to tissue components in vivo

Author information

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Abstract

Adult male rats were given an oral dose of 10 mg/kg aspartame 14C-labelled in the methanol carbon. At timed intervals of up to 6 hours, the radioactivity in plasma and several organs was investigated. Most of the radioactivity found (>98% in plasma, >75% in liver) was bound to protein. Label present in liver, plasma and kidney was in the range of 1-2% of total radioactivity administered per g or mL, changing little with time. Other organs (brown and white adipose tissues, muscle, brain, cornea and retina) contained levels of label in the range of 1/12 to 1/10th of that of liver. In all, the rat retained, 6 hours after administration about 5% of the label, half of it in the liver. The specific radioactivity of tissue protein, RNA and DNA was quite uniform. The protein label was concentrated in amino acids, different from methionine, and largely coincident with the result of protein exposure to labelled formaldehyde. DNA radioactivity was essentially in a single different adduct base, different from the normal bases present in DNA. The nature of the tissue label accumulated was, thus, a direct consequence of formaldehyde binding to tissue structures. The administration of labelled aspartame to a group of cirrhotic rats resulted in comparable label retention by tissue components, which suggests that liver function (or its defect) has little effect on formaldehyde formation from aspartame and binding to biological components. The chronic treatment of a series of rats with 200 mg/kg of non-labelled aspartame during 10 days resulted in the accumulation of even more label when given the radioactive bolus, suggesting that the amount of formaldehyde adducts coming from aspartame in tissue proteins and nucleic acids may be cumulative. It is concluded that aspartame consumption may constitute a hazard because of its contribution to the formation of formaldehyde adducts.

http://www.ncbi.nlm.nih.gov/pubmed/9714421

Environmental Health Perspectives • February 1997

Reproductive toxicology—Sodium Saccharin—CAS#128-44-9 0

Swiss CD-1 mice, at 0.0, 1.25, 2.5, and 5.0% in water

James Lamb IV, NTP/NIEHS, Project Officer
Dushyant Gulati, Valerie Russell, Leta Hommel, K. Poonacha and P. Sabharwal, Environmental Health Research and Testing Started 7/1/82 and Completed 2/20/85

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1470282/pdf/envhper00326-0340.pdf

Sodium Saccharin

CAS #128-44-9
Swiss CD-1 mice, at 0.0, 1.25, 2.5, and 5.0% in water
James Lamb IV, NTP/NIEHS Project Officer,
Dushyant Gulati, Valerie Russell, Leta Hommel, K. Poonacha, and
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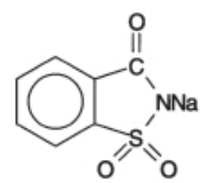
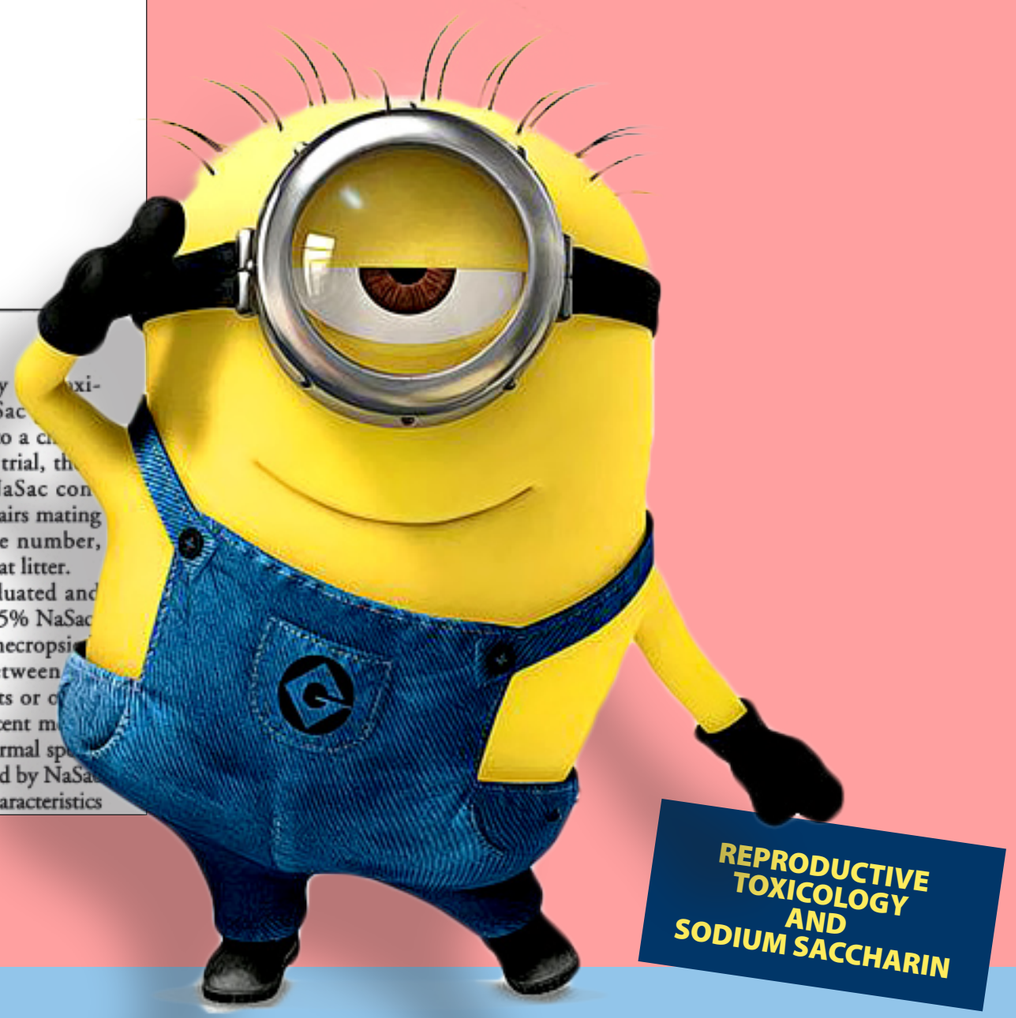
NTIS #PB85188258/AS



Sodium saccharin (NaSac), used as an artificial sweetener since the late 1800s, was tested for potential effects on reproduction and fertility in Swiss CD-1 mice using the RACB protocol (Morrissey et al., Fundam Appl Toxicol 13:747–777 [1989]). Data on food and water consumptions, body weights, and clinical signs from the dose-range-finding study (Task 1) were used to set exposure concentrations for the continuous cohabitation phase (Task 2) at 1.25, 2.5, and 5% weight per volume in the drinking water. While water consumption was decreased at the high dose by approximately 10 to 20%, it was increased at the low and middle dose levels by approximately 40 and 20%, respectively. increased mortality at 5% NaSac was attributed to complications of dehydration. For the surviving pairs, there was no reduction in the mean number of litters per pair, although at the high dose, the number of live pups per litter decreased by 16% and the pup weight adjusted for litter size was decreased by 6%. There was no decrease in the viability of the offspring.

These effects were considered secondary to the decreased water intake seen at the high dose, and since the middle dose level had a relative increase in intake and showed no reproductive toxicity, Task 2 was judged to be essentially negative for reproductive toxicity, and the evaluation of the second generation was performed with consumption was increased by [illegible]xi-mately 20% in the 2.5% NaSac [illegible] although this did not translate to a ch[illegible] in body weight. In the mating trial, th[illegible] were no differences due to NaSac con[illegible]sumption in the percent of F_1 pairs mating or delivering a litter, or in the number, weight, or viability of pups in that litter.

After the F_2 pups were evaluated and discarded, the F_1 controls and 2.5% NaSac exposed mice were killed and necropsi[illegible] There were no differences between [illegible] groups in terminal body weights or o[illegible] weights. The concentration, percent m[illegible] or percent morphologically abnormal sp[illegible] in the epididymis were unchanged by NaSac exposure, as was the length or characteristics



“Doses of 15, 30, 60, 450, 1500 and 2250 mg of acesulfame-K/kg [of] body weight **induced a positive dose-dependent significant clastogenicity.** These doses were within the no-toxic-effect levels reported by the Joint Expert Committee for Food Additives of the World Health Organization and the Food and Agriculture Organization of the United Nations.”

Food Chemistry And Toxicology • December 1997

In vivo cytogenetic studies on mice exposed to acesulfame-K—a non-nutritive sweetener

Author information

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Abstract

Acesulfame-K, a sweetening agent, was evaluated in vivo for its genotoxic and clastogenic potentials. Swiss albino male mice were exposed to the compound by gavage. Bone marrow cells isolated from femora were analysed for chromosome aberrations. Doses of 15, 30, 60, 450, 1500 and 2250 mg of acesulfame-K/kg body weight induced a positive dose-dependent significant clastogenicity (trend test alpha < 0.05). These doses were within the no-toxic-effect levels (1.5-3 g/kg body weight in rats) reported by the Joint Expert Committee for Food Additives of the World Health Organization and the Food and Agriculture Organization of the United Nations. In view of the present significant in vivo mammalian genotoxicity data, acesulfame-K should be used with caution.

http://www.ncbi.nlm.nih.gov/pubmed/9449223

~ This Peer Reviewed Report Is Almost 20 Years Old ~

CLASTOGENICITY

In biology a clastogen is a mutagenic agent giving rise to inducing or causing the breakage or disruption of chromosomes leading to sections of the chromosomes being deleted, added or rearranged. This process, a form of mutagenesis, can lead to carcinogenesis or cancer. Exposure increases the frequency of abnormal cells in paternal males which contributes to developmental effects in the fetus during fertilization and growth.

“Eleven percent of healthy preschoolers consumed > or = 12 fl oz/day of fruit juice, which is considered excessive. Excess fruit juice consumption has been reported as a contributing factor in some children with nonorganic failure to thrive and in some children with decreased stature. In other children, excessive fruit juice consumption has been associated with an increased caloric intake and obesity.”

Journal Of The American College Of Nutrition • October 1996

Fruit juice consumption by infants and children: a review

By B. A. Dennison
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Abstract

The pattern of fruit juice consumption has changed over time. Fifty years ago, orange juice was the major juice produced and it was consumed primarily to prevent scurvy. Now, apple juice is the juice of choice for the under 5 age group. While fruit juice is a healthy, low-fat, nutritious beverage, there have been some health concerns regarding juice consumption. Nursing bottle caries have long been recognized as a consequence of feeding juice in bottles, using the bottle as a pacifier, and prolonged bottle feeding. Non-specific chronic diarrhea or “toddler’s” diarrhea has been associated with juice consumption, especially juices high in sorbitol and those with a high fructose to glucose ratio. This relates to carbohydrate malabsorption, which varies by the type, concentration, and mixture of sugars present in different fruit juices. Fruit juice consumption by preschoolers has recently increased from 3.2 to about 5.5 fl oz/day. Consumption of fruit juice helps fulfill the recommendation to eat more fruits and vegetables, with fruit juice accounting for 50% of all fruit servings consumed by children, aged 2 through 18 years, and 1/3 of all fruits and vegetables consumed by preschoolers. Concomitant with the increase in fruit juice consumption has been a decline in milk intake. This is concerning as milk is the major source of calcium in the diet, and at present, only 50% of children, aged 1 through 5 years, meet the RDA for calcium. Studies of newborn infants and preschool-aged children have demonstrated a preference for sweet-tasting foods and beverages. Thus, it is not surprising that some children, if given the opportunity, might consume more fruit juice than is considered optimal. Eleven percent of healthy preschoolers consumed > or = 12 fl oz/day of fruit juice, which is considered excessive. Excess fruit juice consumption has been reported as a contributing factor in some children with nonorganic failure to thrive and in some children with decreased stature. In other children, excessive fruit juice consumption has been associated with an increased caloric intake and obesity. This paper reviews the role of fruit juice in the diets of infants and children and outlines areas for future research. Recommendations regarding fruit juice consumption based on current data are also given.

http://www.ncbi.nlm.nih.gov/pubmed/8892177

ERYTHRITOL

Erythritol ((2R,3S)-butane-1,2,3,4-tetraol) is a sugar alcohol (or polyol) that has been approved for use as a food additive in the United States and throughout much of the world. It was discovered in 1848 by Scottish chemist John Stenhouse. It occurs naturally in some fruit and fermented foods. At the industrial level, it is produced from glucose by fermentation with a yeast, Moniliella pollinis. Erythritol is 60–70% as sweet as sucrose (table sugar), yet it is almost noncaloric, does not affect blood sugar, does not cause tooth decay, and is partially absorbed by the body, excreted in urine and feces. Under U.S. Food and Drug Administration (FDA) labeling requirements, it has a caloric value of 0.2 kilocalories per gram (95% less than sugar and other carbohydrates), though nutritional labeling varies from country to country. Some countries, such as Japan and the United States, label it as zero-calorie, while the European Union currently labels it at 0 kcal/gram.

Erythritol And Human Digestion

In the body, most erythritol is absorbed into the bloodstream in the small intestine, and then for the most part excreted unchanged in the urine. About 10% enters the colon. Because 90% of erythritol is absorbed before it enters the large intestine, it does not normally cause laxative effects, as are often experienced after consumption of other sugar alcohols (such as xylitol. mannitol and maltitol), although extremely large doses can cause nausea and borborygmi (stomach rumbling).

Side Effects

In general, erythritol can cause a significant increase in nausea and stomach rumbling (borborygmi). Rarely, erythritol can cause allergic hives (urticaria). When compared with other sugar alcohols, it is also much more difficult for intestinal bacteria to digest, so it is less likely to cause gas or bloating more than other polyols, such as maltitol, sorbitol, or lactitol.

Blending For Sugar-Like Properties With Stevia

Erythritol is commonly used as a medium in which to deliver high-intensity sweeteners, especially stevia derivatives, serving the dual function of providing both bulk and a flavor similar to that of table sugar. Diet beverages made with this blend, thus, contain erythritol in addition to the main sweetener. Beyond high-intensity sweeteners, erythritol is often paired with other bulky ingredients that exhibit sugar-like characteristics to better mimic the texture and mouthfeel of sucrose. The cooling effect of erythritol is rarely desired, hence other ingredients are chosen to dilute or negate that effect. Erythritol also has a propensity to crystallize and is not as soluble as sucrose, so ingredients may also be chosen to help negate this disadvantage. Furthermore, erythritol is not hygroscopic, meaning it does not attract moisture, which can lead to the drying out of products, in particular baked goods, if another hygroscopic ingredient is not used in the formulation. Inulin is often combined with erythritol because of inulin's offering a complementary negative heat of solution (exothermic, or warming effect when dissolved, which helps cancel erythritol's cooling effect) and noncrystallizing properties. However, inulin has a propensity to cause gas and bloating in those having consumed it in moderate to large quantities, in particular in individuals unaccustomed to it. Other sugar alcohols are sometimes used with erythritol, in particular isomalt, because of its minimally positive heat of solution, and glycerin, which has a negative heat of solution, moderate hygroscopicity, and noncrystallizing liquid form. Erythritol is tooth-friendly; it cannot be metabolized by oral bacteria, so it does not contribute to tooth decay.

“an exceedingly high incidence of brain tumors in aspartame-fed rats”

Journal Of Neuropathology And Experimental Neurology • November 1996

Increasing brain tumor rates: is there a link to aspartame?

Author information

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Abstract

In the past two decades brain tumor rates have risen in several industrialized countries, including the United States. During this time, brain tumor data have been gathered by the National Cancer Institute from catchment areas representing 10% of the United States population. In the present study, we analyzed these data from 1975 to 1992 and found that the brain tumor increases in the United States occurred in two distinct phases, an early modest increase that may primarily reflect improved diagnostic technology, and a more recent sustained increase in the incidence and shift toward greater malignancy that must be explained by some other factor(s). Compared to other environmental factors putatively linked to brain tumors, the artificial sweetener aspartame is a promising candidate to explain the recent increase in incidence and degree of malignancy of brain tumors. Evidence potentially implicating aspartame includes an early animal study revealing an exceedingly high incidence of brain tumors in aspartame-fed rats compared to no brain tumors in concurrent controls, the recent finding that the aspartame molecule has mutagenic potential, and the close temporal association (aspartame was introduced into US food and beverage markets several years prior to the sharp increase in brain tumor incidence and malignancy). We conclude that there is need for reassessing the carcinogenic potential of aspartame.

Full text, PDF, graphs, charts and 25 references

http://jnen.oxfordjournals.org/content/jnen/55/11/1115.full.pdf

Carcinogenesis • November 1995

Effects of sodium ascorbate, sodium saccharin and ammonium chloride on the male rat urinary bladder

Author information

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> “Sodium saccharin administered at high doses to male rats beginning after 5 weeks of age produces mild urothelial hyperplasia but does not result in a significant increase in incidence of bladder cancer unless it is administered after an initiating agent. However, if it is administered in a two-generation bioassay, a significant incidence of bladder tumors is produced.”

Abstract

Sodium saccharin administered at high doses to male rats beginning after 5 weeks of age produces mild urothelial hyperplasia but does not result in a significant increase in incidence of bladder cancer unless it is administered after an initiating agent. However, if it is administered in a two-generation bioassay, a significant incidence of bladder tumors is produced. The hyperplastic and tumorigenic effects are inhibited by co-administration with high doses of NH4Cl. The present experiment was designed to evaluate the effects of another sodium salt, sodium ascorbate, administered through the neonatal time period. Sodium saccharin administered as 5% of the diet produced urothelial hyperplasia and increased labeling index, and this was inhibited by co-administration with 1.23% NH4Cl. Four doses of sodium ascorbate was evaluated. The lowest dose, 0.91%, was without effect on the urinary tract. A slight effect (not statistically significant) was observed at a dose of 2.73%, and a significant proliferative response was detected at 4.56 and 6.84%. Recent studies suggest that a calcium phosphate-containing amorphous precipitate forms in the urine of rats fed high doses of sodium saccharin, producing cytotoxicity of the urothelium and consequent regenerative hyperplasia. This precipitate was observed in the present experiment in the rats administered the high dose of sodium saccharin or the higher doses of sodium ascorbate. Formation of this precipitate and induction of urothelial proliferation were inhibited by co-administration of NH4Cl, but somewhat higher doses of ammonium chloride were required for doses of sodium ascorbate compared to sodium saccharin. These results demonstrate that sodium ascorbate administered through the neonatal time period of the male rat produces urothelial hyperplasia in the dose responsive manner, with a no-effect level of 0.91% of the diet. The formation of the calcium phosphate-containing amorphous precipitate and urothelial proliferation were inhibited by co-administration with NH4Cl.

http://www.ncbi.nlm.nih.gov/pubmed/7586194

“The increases in the levels of urinary organic acids in the polyol-fed rats were explained in terms of impaired mitochondrial oxidation of these acids and of impaired conversion of methylmalonic acid to succinic acid.”

Toxicology And Applied Pharmacology • September 1987

Organic aciduria in rats fed high amounts of xylitol or sorbitol

By M.M. Hämäläinen

Abstract

The acidification of urine during polyol feeding was investigated with 27 Long-Evans male rats (aged 12 weeks) which were fed a xylitol diet (X), a sorbitol diet (S), or a basal diet for 4 weeks. The amount of polyols in the diet was increased from 5% to the final 20% level within 3 weeks. The polyol-fed animals showed reduced weight gain, lowered urine pH (from 6.5 to 5.6), and a 4-fold increase in the titratable acid excretion. X and S increased the daily urine volumes by 49 and 63%, respectively, but did not affect the wet weight or the pH values of the feces. as chromatographic-mass spectrometric analyses of organic acids revealed highly increased amounts of methylmalonic acid (13- to 20-fold) and 2-oxoglutaric acid (4- to 5-fold) in the urine of polyol-fed rats. The urinary excretion of citric acid and malic acid was also increased significantly (2- to 4-fold). The acidity of urine was not reflected in the blood acid-base balance of the animals. The increases in the levels of urinary organic acids in the polyol-fed rats were explained in terms of impaired mitochondrial oxidation of these acids and of impaired conversion of methylmalonic acid to succinic acid.

http://www.ncbi.nlm.nih.gov/pubmed/3629597

“Such observed alterations in brain neurotransmitter concentrations may be responsible for the reported clinical and behavioral effects associated with Aspartame ingestion.”

Toxicology And Applied Pharmacology • March 1986

Neurobiochemical alterations induced by the artificial sweetener aspartame (NutraSweet)

Coulombe RA Jr, Sharma RP.

Abstract

The dipeptide aspartame (NutraSweet) is a newly approved and widely used artificial sweetener in foods and beverages. Consumption of aspartame (ASM) has been reported to be responsible for neurologic and behavioral disturbances in sensitive individuals. Unfasted male CD-1 mice were dosed orally with 13, 130, or 650 mg/kg ASM in corn oil, while control animals received corn oil alone. Three hours after dosing, the animals were killed, and the concentrations of the catecholamines norepinephrine (NE) and dopamine (DA), catecholamine metabolites 3-methoxy-4-hydroxymandelic acid (VMA), homovanillic acid (HVA), and dihydroxyphenylacetic acid (DOPAC), the indoleamine serotonin (5-HT), and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were determined by electrochemical high-performance liquid chromatography in six brain regions. ASM exerted its primary effect on adrenergic neurotransmitters in various brain regions. In the hypothalamus, the region richest in NE, increases in NE concentrations of 12, 49, and 47% were found in the low, medium, and high dose groups, respectively, relative to control. Significant increases of NE in the medulla oblongata and corpus striatum were also observed. Increases of the catecholamine DA and catecholamine metabolites VMA, HVA, and DOPAC were seen in various regions. The indoleamine serotonin and its metabolite 5-HIAA were unaffected by ASM treatment. These findings are consistent with ASM-induced increases in the brain catecholamine precursor amino acids phenylalanine and tyrosine, as reported earlier. Such observed alterations in brain neurotransmitter concentrations may be responsible for the reported clinical and behavioral effects associated with ASM ingestion.

http://www.ncbi.nlm.nih.gov/pubmed/2420032

“The diuretic effect of the polyols was considered responsible for the changes in the monovalent ion metabolism. The alterations in the excretion of multivalent cations most likely resulted from their increased intestinal absorption facilitated by the general chelating action of these polyols.”

The Journal Nutrition • April 1986

Alterations in electrolyte and iron metabolism in the rat in relation to peroral administration of galactitol, mannitol and xylitol

By M.M. Hämäläinen MM and K.K. Mäkinen

Abstract

Groups of 12 Long-Evans male rats were exposed to diets containing 20% galactitol (G), mannitol (M) or xylitol (X) for 5 wk. Serum electrolyte concentrations were within normal ranges for rats in all groups compared to control rats. All polyol-fed animals exhibited diuresis and a lower urinary pH (6.2-5.3) with a concomitant lower excretion of Na+, Cl- and protein (40% of controls). The excretion of K+ was lower in the X-fed rats than in any other group. Urinary Ca2+ excretion was sixfold higher and Mg2+ excretion, twofold higher in all polyol-fed rats than in controls. PO4 and NH4+ excretions were higher than controls in G- and M-fed animals only. Serum aldosterone concentrations in all polyol rats were 60% of those in controls. The serum corticosterone and parathyroid hormone levels were normal. Urinary citric acid was significantly higher in rats fed polyols but oxalic acid excretion was either normal (X) or lower (G,M) than in controls. Concentrations of serum and liver iron were higher in polyol-fed rats than in controls. Nevertheless, the normal serum creatinine and electrolyte concentrations and normal urinary creatinine levels established healthy kidney function. The diuretic effect of the polyols was considered responsible for the changes in the monovalent ion metabolism. The alterations in the excretion of multivalent cations most likely resulted from their increased intestinal absorption facilitated by the general chelating action of these polyols.

http://www.ncbi.nlm.nih.gov/pubmed/3083056

“... all three polyols retarded the growth rate of the animals ... those fed galactitol or mannitol had lower blood glucose, and those fed mannitol had higher blood pyruvic acid ... Rats fed any of the polyols had lower serum total cholesterol and liver ascorbic acid than control rats.”

http://www.ncbi.nlm.nih.gov/pubmed/3925094

The Journal Of Nutrition • July 1985

Metabolic effects in rats of high oral doses of galactitol, mannitol and xylitol

By K.K. Mäkinen and M.M. Hämäläinen

Abstract

The effect of feeding high amounts of polyols on rat metabolism was studied. Adult male rats were fed the basal diet or the same diet to which had been added either galactitol, mannitol or xylitol for 8 wk (final polyol level 200 g/kg diet). Although all three polyols retarded the growth rate of the animals, the polyols were well tolerated. The four experimental groups did not differ significantly (P greater than 0.01) in the following analyses: blood lactic acid and serum transaminases, amylase, lactate dehydrogenase, triglycerides, insulin, glucagon and corticosterone. Compared to rats fed the basal diet, galactitol rats had higher blood hemoglobin levels (P less than 0.01); those fed galactitol or mannitol had lower blood glucose (P less than 0.001 and P less than 0.01, respectively), and those fed mannitol had higher blood pyruvic acid (P less than 0.01). Rats fed any of the polyols had lower serum total cholesterol and liver ascorbic acid (P less than 0.001) than control rats. Rats fed mannitol had higher liver glycogen levels (P less than 0.001) than control rats. Irrespective of the structural differences between the pentitol and the hexitols, a number of common metabolic effects were found. The proposed mechanisms of these effects include 1) the slow absorption and the rapid intraluminal metabolism of the polyols and 2) the similar handling of these polyols in the liver by a dehydrogenase.

Neurobehavior, Toxicology And Teratology • November 1984

Excitotoxic food additives—relevance of animal studies to human safety

By JW Olney

Abstract - Over 20 Years Old

"Evidence is reviewed supporting the view that excitotoxic food additives pose a significant hazard to the developing nervous system of young children. The following points are stressed: (1) although blood-brain barriers protect most central neurons from excitotoxins, certain brain regions lack such protection (a characteristic common to all vertebrate species); (2) regardless of species, it requires only a transient increase in blood excitotoxin levels for neurons in unprotected brain regions to be "silently" destroyed; (3) humans may be at particularly high risk for this kind of brain damage, since ingestion of a given amount of excitotoxin causes much higher blood excitotoxin levels in humans than in other species; (4) in addition to the heightened risk on a species basis, risk may be further increased for certain consumer sub-populations due to youth, disease or genetic factors; (5) despite these reasons for maintaining a wide margin of safety in the use of excitotoxins in foods, no safety margin is currently being observed, i.e., a comparative evaluation of animal (extensive) and human (limited) data supports the conclusion that excitotoxins, as used in foods today, may produce blood elevations high enough to cause damage to the nervous system of young children, damage which is not detectable at the time of occurrence but which may give rise to subtle disturbances in neuroendocrine function in adolescence and/or adulthood."

http://www.ncbi.nlm.nih.gov/pubmed/6152304

“Three two-generation studies using saccharin have since been conducted. The results from these studies clearly show that when rats were exposed to diets containing 5 or 7.5% sodium saccharin from the time of conception to death, an increased frequency of urinary bladder cancers was found, predominantly in the males.”

Environmental Health Perspectives • April 1983

Two-generation saccharin bioassays

D L Arnold

Abstract

The controversy regarding the safety of saccharin for human consumption started shortly after its discovery over 100 years ago and has yet to subside appreciably. The consumption of saccharin, particularly in North America, began to escalate when the U.S. Food and Drug Administration set new standards of identity which allowed foods containing artificial sweeteners to be promoted as “nonnutritive” or “noncaloric” sweeteners for use by the general public. In 1969, when cyclamates were banned, at least 10 single-generation feeding studies were undertaken with saccharin to more accurately assess the potential toxicological consequences resulting from the anticipated increase in its consumption. None of these studies resulted in any overt regulatory action. Subsequently, the introduction of the two-generation chronic toxicity/carcinogenicity bioassay added a new tool to the toxicologist’s arsenal. Three two-generation studies using saccharin have since been conducted. The results from these studies clearly show that when rats were exposed to diets containing 5 or 7.5% sodium saccharin from the time of conception to death, an increased frequency of urinary bladder cancers was found, predominantly in the males. While some study results suggested that impurities in commercial saccharin or the presence of urinary tract calculi may have been responsible for the observed bladder tumors, it now appears that these possibilities are highly unlikely. The mechanism by which saccharin elicited the bladder tumors using the two-generation experiment has not been ascertained.

Full text with 37 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1569221/

“Two-year feeding experiments in mice and rats indicated possible carcinogenicity of a high-percentage xylitol diet. Abnormalities of cellular growth were also documented in animals fed high percentages of sorbitol and sucrose. Long-term mannitol feeding experiments also revealed an increased incidence of benign thymic tumors in rats. Intravenous feeding of fructose, xylitol, and sorbitol causes major concern. The toxicity is total-dose and infusion-rate dependent. The physical toxicity induced by hyperosmolar effect of the concentrated infusion solutions can be lethal.”

Annual Review Of Nutrition • July 1981

Nutritional significance of fructose and sugar alcohols

By Y.M. Wang YM and J. van Eys

Abstract

Human metabolism of D-fructose, D-sorbitol, D-mannitol, and xylitol has been documented. In humans, sorbitol and xylitol at a single oral dose of 20 g or less and fructose at 70 g or less most likely can be fully absorbed. These there sugars can maintain, either independently or nearly independently, the integrity or the carbohydrate requirement for the growth of cells and animals. The absorption of D-mannitol is no more than 80% and is more laxative. In general, there is no adverse effect other than osmotic diarrhea after oral administration of these sugars. Transient hyperuricemia was seen in some humans. The chronic toxicity of life-long usage of these sugars in humans or other primates is not known. However, a 2-year Turku sugar studies suggested the safety of fructose and xylitol. Two-year feeding experiments in mice and rats indicated possible carcinogenicity of a high-percentage xylitol diet. Abnormalities of cellular growth were also documented in animals fed high percentages of sorbitol and sucrose. Long-term mannitol feeding experiments also revealed an increased incidence of benign thymic tumors in rats. Intravenous feeding of fructose, xylitol, and sorbitol causes major concern. The toxicity is total-dose and infusion-rate dependent. The physical toxicity induced by hyperosmolar effect of the concentrated infusion solutions can be lethal. The primary metabolic toxicities, mainly lactic acidosis and hypruricemia, are reversible. The suggested safe infusion rate of these sugars is 0.25 g/kg/h; sporadic toxic observations have been reported at this or lower doses (0.125 g/kg/h). The combination of glucose, fructose, xylitol, and sorbitol mixture intravenously is in use in Europe due to the critical threshold of each element. There are positive findings from the use of the combination in human illness (114). The beneficial effect of xylitol, mannitol, sorbitol, and fructose in decreasing order has been well documented in the prevention of dental caries in animals and in humans. Oral organisms do not appear to metabolically adapt to xylitol even after 4 years of in vivo exposure. This was based on the quantitation of xylitol dehydrogenase activity in saliva and oral organisms. In addition, a therapeutic and preventive effect for xylitol in human and animal dental caries has been demonstrated. There appears to be at least a theoretical edge in the dietary use of fructose, xylitol, and sorbitol in diabetics.

http://www.ncbi.nlm.nih.gov/pubmed/6821187

“... the particularly slow passive absorption of sorbitol and xylitol can sometimes be a disadvantage, since osmotic diarrhoea may occur after administration of high oral doses.”

Internationale Zeitschrift Fur Vitamin Und Ernahrungsforschung Beiheft • July 1976

Sugar substitutes in the diabetic diet

By H. Mehnert

Abstract

The decreased glucsoe utilization in diabetes mellitus justifies the use of sugar substitutes (“diabetic sugar”) if two conditions are fulfilled: 1)The sugar substitute should be a carbohydrate which does not lead, or only to a slight degree, to hyperglycaemia and thus, in this respect, differs distinctly from sugars such as glucose and saccharose. 2) The sugar substitute must not cause undesired side-effects. The absorption, utilization and side-effects of the sugar substitutes fructose, sorbitol and xylitol were investigated. They were found to be more slowly absorbed than glucose and thus to offer the advantage of better utilization under conditions of limited insulin production. However, the particularly slow passive absorption of sorbitol and xylitol can sometimes be a disadvantage, since osmotic diarrhoea may occur after administration of high oral doses. The sugar substitutes enter the metabolism enzymatically and are utilized mainly in the liver. The peripheral state was investigated after intravenous, intraduodenal and oral administration of glucose and fructose to healthy subjects. Liver metabolism was examined (Dietze) by comparing hepatic venous and arterial concentrations after intravenous administration of the sugars. Also, diabetic patients received glucose and fructose orally. As previously demonstrated, the investigations using several techniques showed a smaller influence on blood glucose and serum insulin concentrations after administration of fructose, sorbitol and xylitol than after glucose. If no metabolic changes occur after intravenous administration of high doses, no such changes need be expected after oral administration of small doses. Nor did measurements in hepatic venous blood (Dietze) show any marked effect of fructose on the blood glucose level. The healthy subjects showed no significant changes in blood glucose or serum insulin concentration after either intraduodenal or oral administration of fructose, whereas they showed a considerable increase after glucose administration. Investigations in adult-type diabetics revealed a better utilization of fructose than glucose. With correct dosage, sugar substitutes are able to increase the carbohydrate tolerance and, under certain conditions, to achieve a relative stabilization of the metabolism of unstable diabetics. The antiketogenic activity of sugar substitutes is particularly pronounced. Side-effects such as high blood levels of urea, lactate, triglycerides and bilirubin or a decrease in hepatic adenin nucleotides do not occur after oral administration, nor are they of importance after intravenous administration with correct dosage. The osmotic diarrhoea occurring after intake of sorbitol or xylitol is caused by their slow absorption and limits the consumption of these sugar substitutes. In the often obese adult-type diabetics, the calorie intake inherent in the consumption of diabetic sugars may have an unfavourable influence on their weight...

http://www.ncbi.nlm.nih.gov/pubmed/783058

CHAPTER SEVEN

Acrylamide

The Peer Review

Polyacrylamide and acrylamide copolymers are used in many industrial processes, such as the production of paper, dyes, and plastics, and in the treatment of drinking water and wastewater, including sewage. They are also found in consumer products, such as caulking, food packaging, and some adhesives. Trace amounts of acrylamide generally remain in these products.

Researchers in Europe and the United States have found acrylamide in certain foods that were heated to a temperature above 120° Celsius (248° Fahrenheit), but not in foods prepared below this temperature although most foods require cooking at temperatures above 120°. Potato chips and French fries were found to contain higher levels of acrylamide compared with other foods. The World Health Organization and the Food and Agriculture Organization of the United Nations stated that the levels of acrylamide in foods pose a "*major concern*" and that more research is needed to determine the risk of dietary acrylamide exposure. Some of that research is here.

Asparagine is an amino acid (a building block of proteins) that is found in many vegetables, with higher concentrations in some varieties of potatoes. When heated to high temperatures in the presence of certain sugars, asparagine can form acrylamide. High-temperature cooking methods, such as frying, baking, or broiling, have been found to produce acrylamide, while boiling and steaming appear less likely to do so. Longer cooking times can also increase acrylamide production when the cooking temperature is above 120° C.

Decreasing cooking time, blanching potatoes before frying, and postdrying (drying in a hot air oven after frying) have been shown to produce a limited decrease in the acrylamide content of some foods.

Acrylamide levels in food vary widely depending on the manufacturer, the cooking time, and the method and temperature of the cooking process. The best advice at this time is to follow established dietary guidelines and eat a healthy, balanced diet that is low in fat and rich in high-fiber grains, fruits, vegetables, coconut oil, nuts and seeds. Studies in rodent models have found that acrylamide exposure poses a risk for several types of cancer. However, the evidence from human studies is still less complete but promising. The National Toxicology Program and the International Agency for Research on Cancer consider acrylamide to be a "probable human carcinogen," based on studies in laboratory animals given acrylamide in drinking water.

To accurately determine acrylamide exposure, biomarkers of exposure were recently used in a Danish cohort study designed to evaluate the subsequent risk of breast cancer in postmenopausal women. Among women with higher levels of acrylamide bound to the hemoglobin in their blood, there was a statistically significant increase in risk of estrogen receptor-positive breast cancer. This finding suggests an endocrine hormone-related effect, which would be consistent with the results of a questionnaire-based cohort study in the Netherlands that found an excess of endometrial and ovarian cancer—but not of postmenopausal breast cancer—associated with higher levels of acrylamide exposure. Another cohort study from the Netherlands suggested a positive association between dietary acrylamide and the risk of renal cell cancer, but not necessarily of prostate or bladder cancer.

High levels of acrylamide in the workplace have been shown to cause neurological damage, e.g., among workers using acrylamide polymers to clarify water in coal preparation plants.

The U.S. Environmental Protection Agency (EPA) regulates acrylamide in drinking water. The EPA established an acceptable level of acrylamide exposure, set low enough to account for any uncertainty in the data relating acrylamide to cancer and neurotoxic effects. The U.S. Food and Drug Administration regulates the amount of residual acrylamide in a variety of materials that come in contact with food, but there are currently no guidelines governing the presence of acrylamide in food itself.

“Acrylamide (AA) and its metabolites have been recognized as potential carcinogens, but also they can cause other negative symptoms in human or animal organisms and therefore this class of chemical compounds has attracted a lot of attention. These substances are usually formed when heating [food] ...”

Food & Function • February 2016

A review of the interactions between acrylamide, microorganisms and food components

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Abstract

Acrylamide (AA) and its metabolites have been recognized as potential carcinogens, but also they can cause other negative symptoms in human or animal organisms and therefore this class of chemical compounds has attracted a lot of attention. These substances are usually formed when heating asparagine in the presence of compounds that have a-hydroxycarbonyl groups, a,ß,y,o-diunsaturated carbonyl groups or a-dicarbonyl groups. The acrolein pathway and enzymatic decarboxylation of asparagine, as well as endogenic processes, are other alternative routes to AA formation. It has been demonstrated that the animal model used for examining AA toxicity may not be sufficient to investigate these changes in humans, therefore it is necessary to design an in vitro model, which could provide more accurate insights into the direction of these processes in human organisms. Acrylamide can be metabolized through both oxidative and reductive pathways; moreover, there is also a chance that some representatives of intestinal microbiota are able to transform acrylamide. It was shown that there are various microorganisms, mostly bacteria, that produce amidases, i.e. enzymes decomposing AA. Lactic acid bacteria also appear to demonstrate the ability to use acrylamide as a carbon source, but this still requires further investigation. Another way to prevent AA toxicity is related to the presence of some food compounds, such as certain proteins or polyphenols. There are still lot of gaps in the current knowledge related to AA toxicity, so future potential research directions are presented in this review as well.

http://www.ncbi.nlm.nih.gov/pubmed/26830455

“These results indicate that in weaning rats, acrylamide is positively associated with neurotoxicity in a dose-dependent manner ...”

Neural Regeneration Research • June 2015

Acrylamide neurotoxicity on the cerebrum of weaning rats

Author information
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Lou TY3, Liu SS4, Li GY1.

Abstract

The mechanism underlying acrylamide-induced neurotoxicity remains controversial. Previous studies have focused on acrylamide-induced toxicity in adult rodents, but neurotoxicity in weaning rats has not been investigated. To explore the neurotoxic effect of acrylamide on the developing brain, weaning rats were gavaged with 0, 5, 15, and 30 mg/kg acrylamide for 4 consecutive weeks. No obvious neurotoxicity was observed in weaning rats in the low-dose acrylamide group (5 mg/kg). However, rats from the moderate- and high-dose acrylamide groups (15 and 30 mg/kg) had an abnormal gait. Furthermore, biochemical tests in these rats demonstrated that glutamate concentration was significantly reduced, and y-aminobutyric acid content was significantly increased and was dependent on acrylamide dose. Immunohistochemical staining showed that in the cerebral cortex, y-aminobutyric acid, glutamic acid decarboxylase and glial fibrillary acidic protein expression increased remarkably in the moderate- and high-dose acrylamide groups. These results indicate that in weaning rats, acrylamide is positively associated with neurotoxicity in a dose-dependent manner, which may correlate with upregulation of y-aminobutyric acid and subsequent neuronal degeneration after the initial acrylamide exposure.

Full Text, Graphs, Charts and 27 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4498356/

“Methods to reduce acrylamide levels ... [including] multiorgan toxicity, antifertility, carcinogenicity, neurotoxicity, [and] teratogenicity [are discussed].”

Food Function • June 2015

Acrylamide: inhibition of formation in processed food and mitigation of toxicity in cells, animals, and humans

By M. Friedman

Abstract

Potentially toxic acrylamide is largely derived from the heat-inducing reactions between the amino group of the amino acid asparagine and carbonyl groups of glucose and fructose in plant-derived foods including cereals, coffees, almonds, olives, potatoes, and sweet potatoes. This review surveys and consolidates the following dietary aspects of acrylamide: distribution in food, exposure and consumption by diverse populations, reduction of the content in different food categories, and mitigation of adverse in vivo effects. Methods to reduce acrylamide levels include selecting commercial food with a low acrylamide content, selecting cereal and potato varieties with low levels of asparagine and reducing sugars, selecting processing conditions that minimize acrylamide formation, adding food-compatible compounds and plant extracts to food formulations before processing that inhibit acrylamide formation during processing of cereal products, coffees, teas, olives, almonds, and potato products, and reducing multiorgan toxicity (antifertility, carcinogenicity, neurotoxicity, teratogenicity). The herein described observations and recommendations are of scientific interest for food chemistry, pharmacology, and toxicology, but also have the potential to benefit nutrition, food safety, and human health.

http://www.ncbi.nlm.nih.gov/pubmed/25989363

“Nowadays, the presence of acrylamide in lots of fried and baked foods raises concerns due to its potential to cause toxicity and cancer in animals and human. In this paper, we have criticized all relevant studies in terms of acrylamide mitigation from food by phytochemicals and antioxidants, and the influence of herbal medicines and phyto-pharmaceuticals on reduction of acrylamide toxicity in both animals and human.”

Journal Of Food Science Technology • June 2015

Role of antioxidants and phytochemicals on acrylamide mitigation from food and reducing its toxicity

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Abstract

Nowadays, the presence of acrylamide in lots of fried and baked foods raises concerns due to its potential to cause toxicity and cancer in animals and human. Consequently, a number of papers have focused on evaluation of various chemicals in reduction of acrylamide in various food sources, as well as decreasing its related toxicities. In addition, plants are important sources of diverse metabolites demonstrating either possible effectiveness in acrylamide toxicity or reduction of acrylamide content in food sources. In this paper, we have criticized all relevant studies in terms of acrylamide mitigation from food by phytochemicals and antioxidants, and the influence of herbal medicines and phyto-pharmaceuticals on reduction of acrylamide toxicity in both animals and human.

http://www.ncbi.nlm.nih.gov/pubmed/26028700

“The results of this work add to the known toxic effects of acrylamide and provide a new insight into the possible use of rosemary to ameliorate these effects.”

Tissue & Cell • June 2015

Influence of acrylamide on the gastric mucosa of adult albino rats and the possible protective role of rosemary

Author information

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Abstract

Acrylamide is a common chemical found in heated starchy foods especially potato products. We investigated, for the first time, the effect of acrylamide, alone or with rosemary, on the structure of gastric mucosa of adult male albino rats. Stomach sections were examined using light and scanning electron microscopy. Quantitative immmunohistochemical assessments of the expression of caspase-3, inducible NO synthase (iNOS) and epidermal growth factor receptor (EPGR) were performed. Our results showed that acrylamide produced mucosal erosions and depletion of the protective surface mucus together with widespread inflammatory infiltration. In addition, there was significantly increased expression of caspase-3 and iNOS and weak expression of EPGR. Rosemary exerted a protective effect against acrylamide-induced gastric toxicity via reducing oxidative stress, apoptosis and inflammation as well as accelerating the healing process. The results of this work add to the known toxic effects of acrylamide and provide a new insight into the possible use of rosemary to ameliorate these effects.

http://www.ncbi.nlm.nih.gov/pubmed/25882756

“Acrylamide exerted marked cellular degenerative effects and administration of dark soy sauce and Acrylamide at the same time had neuroprotective effect. Dark soy sauce treatment before Acrylamide exposure gave only marginal improvement.”

Folia Morphol Warszaw • April 2015

Morphological evaluation of the protective role of dark soy sauce against acrylamide induced neurotoxicity in albino rats

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Abstract

BACKGROUND

Acrylamide (ACR) exposure is associated with neurotoxicity, carcinogenicity, and reproductive toxicity. The use of soy sauce as a condiment is common and it has been found that it possesses high antioxidant activity. The objective of the current study is to evaluate the protective role of dark soy sauce (DSS) against ACR-induced neurotoxicity in rats.

MATERIALS AND METHODS

Thirty-five adult male rats were divided into four groups: control, ACR given for 4 weeks, DSS given for 4 weeks before ACR, and DSS given with ACR for 4 weeks. The trigeminal ganglia and cerebellum were dissected and processed for histological staining with haematoxylin and eosin and immunohistochemistry for synaptophysin (SYP) and morphometric analysis.

RESULTS

In the trigeminal ganglia, ACR group showed central chromatolysis, degeneration and cell loss. DSS before ACR group had less marked changes in the neuronal architecture, while in ACR with DSS group, better preservation was observed. In the cerebellum, ACR group showed shrunken Purkinje cells and nuclear pyknosis. Spacing and dissociation between Purkinje layer and other layers was seen. DSS before ACR group showed few degenerated Purkinje cells with normal pattern of the other layers of cerebellar cortex. ACR with DSS group showed less disturbed cerebellar layers architecture. Cerebellar SYP immunoexpression and its area per cent were decreased in ACR group compared with the control. It increased in both DSS treated groups, specifically DSS concomitantly given with ACR.

CONCLUSIONS

ACR exerted marked cellular degenerative effects and administration of DSS and ACR at the same time had neuroprotective effect. DSS treatment before ACR exposure gave only marginal improvement.

http://www.ncbi.nlm.nih.gov/pubmed/25792391

Mutation Research • July 2015

The genetic consequences of paternal acrylamide exposure and potential for amelioration

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Abstract

Acrylamide is a toxin that humans are readily exposed to due to its formation in many carbohydrate rich foods cooked at high temperatures. Acrylamide is carcinogenic, neurotoxic and causes reproductive toxicity when high levels of exposure are reached in mice and rats. Acrylamide induced effects on fertility occur predominantly in males. Acrylamide exerts its reproductive toxicity via its metabolite glycidamide, a product which is only formed via the cytochrome P450 detoxifying enzyme CYP2E1. Glycidamide is highly reactive and forms adducts with DNA. Chronic low dose acrylamide exposure in mice relevant to human exposure levels results in significantly increased levels of DNA damage in terms of glycidamide adducts in spermatocytes, the specific germ cell stage where Cyp2e1 is expressed. Since cells in the later stages of spermatogenesis are unable to undergo DNA repair, and this level of acrylamide exposure causes no reduction in fertility, there is potential for this damage to persist until sperm maturation and fertilisation. Cyp2e1 is also present within epididymal cells, allowing for transiting spermatozoa to be exposed to glycidamide. This could have consequences for future generations in terms of predisposition to diseases such as cancer, with growing indications that paternal DNA damage can be propagated across multiple generations. Since glycidamide is the major contributor to DNA damage, a mechanism for preventing these effects is inhibiting the function of Cyp2e1. Resveratrol is an example of an inhibitor of Cyp2e1 which has shown success in reducing damage caused by acrylamide treatment in mice.

http://www.ncbi.nlm.nih.gov/pubmed/25989052

“Acrylamide is a toxin that humans are readily exposed to due to its formation in many carbohydrate rich foods cooked at high temperatures.

Acrylamide is carcinogenic, neurotoxic and causes reproductive toxicity when high levels of exposure are reached in mice and rats.

This [report findings] could have consequences for future generations in terms of predisposition to diseases such as cancer, with growing indications that paternal DNA damage can be propagated across multiple generations.”

Phytotherapy Research • July 2015

The Potential for Plant Derivatives against Acrylamide Neurotoxicity

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Abstract
Certain industrial chemicals and food contaminants have been demonstrated to possess neurotoxic activity and have been suspected to cause brain-related disorders in humans. Acrylamide (ACR), a confirmed neurotoxicant, can be found in trace amount in commonly consumed human aliments as a result of food processing or cooking. This discovery aroused a great concern in the public, and increasing efforts are continuously geared towards the resolution of this serious threat. The broad chemical diversity of plants may offer the resources for novel antidotes against neurotoxicants. With the goal of attenuating neurotoxicity of ACR, several plants extracts or derivatives have been employed. This review presents the plants and their derivatives that have been shown most active against ACR-induced neurotoxicity, with a focus on their origin, pharmacological activity, and antidote effects.

http://www.ncbi.nlm.nih.gov/pubmed/25886076

“The individual toxic effects of aluminium and acrylamide are well known but there are no data on their combined effects [synergy]. Interestingly, co-exposure to these toxicants exhibited synergism based on physical and biochemical variables in erythrocytes, pro-inflammatory cytokines and DNA damage in liver.”

Chemical And Biological Interactions • July 2015

Disruption of erythrocyte antioxidant defense system, hematological parameters, induction of pro-inflammatory cytokines and DNA damage in liver of co-exposed rats to aluminium and acrylamide

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Abstract

The individual toxic effects of aluminium and acrylamide are well known but there are no data on their combined effects. The present study was undertaken to determine (i) hematological parameters during individual and combined chronic exposure to aluminium and acrylamide (ii) correlation of oxidative stress in erythrocytes with pro-inflammatory cytokines expression, DNA damage and histopathological changes in the liver. Rats were exposed to aluminium (50 mg/kg body weight) in drinking water and acrylamide (20 mg/kg body weight) by gavage, either individually or in combination for 3 weeks. Exposure rats to AlCl3 or/and ACR provoked an increase in MDA, AOPP, H2O2 and a decrease in GSH and NPSH levels in erythrocytes. Activities of catalase, glutathione peroxidase and superoxide dismutase were decreased in all treated rats. Our results showed that all treatments induced an increase in WBC, erythrocyte osmotic fragility and a decrease in RBC, Hb and Ht. While MCV, MCH, MCHC remained unchanged. Hepatic pro-inflammatory cytokines expression including tumor necrosis factor-*a*, interleukin-6, interleukin-1ß was increased suggesting leucocytes infiltration in the liver. A random DNA degradation was observed on agarose gel only in the liver of co-exposed rats to AlCl3 and ACR treatment. Interestingly, co-exposure to these toxicants exhibited synergism based on physical and biochemical variables in erythrocytes, pro-inflammatory cytokines and DNA damage in liver.

http://www.ncbi.nlm.nih.gov/pubmed/25934431

“Dopaminergic system dysfunction is proved to be a possible mechanism in acrylamide-induced neurotoxicity. These results suggest that dopamine levels increase significantly in response to acrylamide, presumably due to changes in the dopamine transport and metabolism related genes expression in the striatal dopaminergic neurons.”

Toxicology Letters • July 2015

Acrylamide increases dopamine levels by affecting dopamine transport and metabolism related genes in the striatal dopaminergic system

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Abstract

Dopaminergic system dysfunction is proved to be a possible mechanism in acrylamide (ACR) -induced neurotoxicity. The neurotransmitter dopamine (DA) has an increasingly important role in the dopaminergic system. Thus, the goal of this study is to evaluate effects of ACR on dopamine and its metabolite levels, dopamine transport and metabolic gene expression in dopaminergic neurons. Male Sprague-Dawley (SD) rats were dosed orally with ACR at 0 (saline), 20, 30, and 40 mg/kg/day for 20 days. Splayed hind limbs, reduced tail flick time and abnormal gait which preceded other neurologic parameters were observed in the above rats. ACR significantly increased dopamine levels, decreased 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA) contents in an area dependent manner in rat striatum. Immunohistochemical staining of the striatum revealed that the number of tyrosine hydroxylase (TH) positive cells significantly increased, while monoamine oxidase (MAO) positive cells were drastically reduced, which was consistent with changes in their mRNA and protein expressions. In addition, dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) expression levels were both down-regulated in the striatum. These results suggest that dopamine levels increase significantly in response to ACR, presumably due to changes in the dopamine transport and metabolism related genes expression in the striatal dopaminergic neurons.

http://www.ncbi.nlm.nih.gov/pubmed/25943760

“Acrylamide (ACR) is a chemical compound with severe neurotoxicity, genotoxicity, carcinogenicity and reproductive toxicity. Recent studies showed that Acrylamide Impairs the function of reproductive organs, e.g., epididymis and testes.”

PLoS One • August 2015

Effect of Acrylamide on Oocyte Nuclear Maturation and Cumulus Cells Apoptosis in Mouse In Vitro

Author information
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Kong F3, Zhang C1, Zhang L1, An L1

Abstract

Acrylamide (ACR) is a chemical compound with severe neurotoxicity, genotoxicity, carcinogenicity and reproductive toxicity. Recent studies showed that ACR impairs the function of reproductive organs, e.g., epididymis and testes. In vitro maturation of mouse oocyte is a sensitive assay to identify potential chemical hazard to female fertility. The aim of this study was to evaluate the adverse effects of ACR on the nuclear maturation and cumulus cells apoptosis of mouse oocytes in vitro. Cumulus-oocyte complexes were incubated in a maturation medium containing 0, 5, 10 and 20 μM of ACR. Chromosome alignment and spindle morphology of oocytes was determined by immunofluorescence and confocal microscopy. Our results showed that oocytes exposed to different doses of ACR in vitro were associated with a significant decrease of oocyte maturation, significant increase of chromosome misalignment rate, occurrence of abnormal spindle configurations, and the inhibition of oocyte parthenogenetic activation. Furthermore, apoptosis of cumulus cells was determined by TUNEL and CASPASE-3 assay. Results showed that apoptosis in cumulus cells was enhanced and the expression of CASPASE-3 was increased after cumulus-oocyte complexes were exposed to ACR. Therefore, ACR may affect the nuclear maturation of oocytes via the apoptosis of cumulus cells in vitro.

Full Text, Graphs, Charts and 65 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537141/

“In a word, mitochondria are a key target at the organelle level for the protective effect of blueberry anthocyanin extract against Acrylamide toxicity.”

Food & Function • September 2015

The chemoprotection of a blueberry anthocyanin extract against theacrylamide-induced oxidative stress in mitochondria: unequivocal evidence in mice liver

Author information
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Abstract

Acrylamide (AA) is one of the most important contaminants occurring in heated food products. Accumulating evidence indicates that AA-induced toxicity is associated with oxidative stress and long-term exposure to AA induced mitochondria collapse and finally leads to apoptosis. Whereas anthocyanins are natural antioxidants and have a strong ability to reduce oxidative damage in vivo. This study investigates the protection of a blueberry anthocyanin extract (BAE) against AA-induced mitochondrial oxidative stress in mice models. The activities of electron transport chain complexes, oxidative status, and the structure and function of mitochondria were measured. Results showed that pretreatment with BAE markedly inhibited reactive oxygen species (ROS) formation, and prevented the successive events associated with the mitochondrial damage and dysfunction, including recovered activities of electron transport chain, ATPase and superoxide dismutase, ameliorated depolarization of mitochondrial membrane potential and membrane lipid peroxidation, reduced release of cytochrome c and protection of mitochondria against swelling. In a word, mitochondria are a key target at the organelle level for the protective effect of BAE against AA toxicity. These results will be helpful to provide new clues for a better understanding of the AA toxicity intervention mechanism and for exploring effective dietary constituents for intervention of AA toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/26190321

Annals Of Chim Acta • September 2015

Comprehensive profiling of mercapturic acid metabolites from dietary acrylamide as short-term exposure biomarkers for evaluation of toxicokinetics in rats and daily internal exposure in humans using isotope dilution ultra-high performance liquid chromatography tandem mass spectrometry

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Abstract

Mercapturic acid metabolites from dietary acrylamide are important short-term exposure biomarkers for evaluating the in vivo toxicity of acrylamide. Most of studies have focused on the measurement of two metabolites, N-acetyl-S-(2-carbamoylethyl)-L-cysteine (AAMA) and N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (GAMA). Thus, the comprehensive profile of acrylamide urinary metabolites cannot be fully understood. We developed an isotope dilution ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) method for the simultaneous determination of all four mercapturic acid adducts of acrylamide and its primary metabolite glycidamide under the electroscopy ionization negative (ESI-) mode in the present study. The limit of detection (LOD) and limit of quantification (LOQ) of the analytes ranged 0.1-0.3 ng/mL and 0.4-1.0 ng/mL, respectively. The recovery rates with low, intermediate and high spiking levels were calculated as 95.5%-105.4%, 98.2%-114.0% and 92.2%-108.9%, respectively. Acceptable within-laboratory reproducibility (RSD<7.0%) substantially supported the use of current method for robust analysis. Rapid pretreatment procedures and short run time (8 min per sample) ensured good efficiency of metabolism profiling, indicating a wide application for investigating short-term internal exposure of dietary acrylamide. Our proposed UHPLC-MS/MS method was successfully applied to the toxicokinetic study of acrylamide in rats. Meanwhile, results of human urine analysis indicated that the levels of N-acetyl-S-(2-carbamoylethyl)-L-cysteine-sulfoxide (AAMA-sul), which did not appear in the mercapturic acid metabolites in rodents, were more than the sum of GAMA and N-acetyl-S-(1-carbamoyl-2-hydroxyethyl)-L-cysteine (iso-GAMA). Thus, AAMA-sul may alternatively become a specific biomarker for investigating the acrylamide exposure in humans. Current proposed method provides a substantial methodology support for comprehensive profiling of toxicokinetics and daily internal exposure evaluations of acrylamide in vivo.

http://www.ncbi.nlm.nih.gov/pubmed/26423628

“acrylamide induces neurotoxic effects in humans and genotoxic, reproductive, and carcinogenic effects in laboratory animals. The results obtained from algal bioassays (Desmodesmus subspicatus and Pseudokirchneriella subcapitata) revealed the toxic effect of acrylamide on these organisms.”

Arhiv za Higijenu Rada i Toksikologiju • December 2015

Assessment of acrylamide toxicity using a battery of standardised bioassays [Procjena toksicdnosti akrilamida pomocu standardiziranih biotestova]

by Zovko M, Vidakovic-Cifrek Z, Cvetkovi K, Bošnir J, Šikic S.

Abstract

Acrylamide is a monomer widely used as an intermediate in the production of organic chemicals, e.g. polyacrylamides (PAMs). Since PAMs are low cost chemicals with applications in various industries and waste- and drinking water treatment, a certain amount of non-polymerised acrylamide is expected to end up in waterways. PAMs are non-toxic but acrylamide induces neurotoxic effects in humans and genotoxic, reproductive, and carcinogenic effects in laboratory animals. In order to evaluate the effect of acrylamide on freshwater organisms, bioassays were conducted on four species: algae Desmodesmus subspicatus and Pseudokirchneriella subcapitata, duckweed Lemna minor and water flea Daphnia magna according to ISO (International Organization for Standardisation) standardised methods. This approach ensures the evaluation of acrylamide toxicity on organisms with different levels of organisation and the comparability of results, and it examines the value of using a battery of low-cost standardised bioassays in the monitoring of pollution and contamination of aquatic ecosystems. These results showed that EC50 values were lower for Desmodesmus subspicatus and Pseudokirchneriella subcapitata than for Daphnia magna and Lemna minor, which suggests an increased sensitivity of algae to acrylamide. According to the toxic unit approach, the values estimated by the Lemna minor and Daphnia magna bioassays, classify acrylamide as slightly toxic (TU=0-1; Class 1). The results obtained from algal bioassays (Desmodesmus subspicatus and Pseudokirchneriella subcapitata) revealed the toxic effect of acrylamide (TU=1-10; Class 2) on these organisms.

http://www.ncbi.nlm.nih.gov/pubmed/26751864

“... neurotoxicologists are concerned about the potential for its cumulative neurotoxicity. It has been shown in several studies that the same neurotoxic effects can be observed at low and high doses of acrylamide, with the low doses simply requiring longer exposures.”

Nutrion & Neuroscience • February 2014

Acrylamide neurotoxicity

Erkekoglu P, Baydar T.

Abstract

Acrylamide, a food contaminant, belongs to a large class of structurally similar toxic chemicals, ‘type-2 alkenes’, to which humans are widely exposed. Besides, occupational exposure to acrylamide has received wide attention through the last decades. It is classified as a neurotoxin and there are three important hypothesis considering acrylamide neurotoxicity: inhibition of kinesin-based fast axonal transport, alteration of neurotransmitter levels, and direct inhibition of neurotransmission. While many researchers believe that exposure of humans to relatively low levels of acrylamide in the diet will not result in clinical neuropathy, some neurotoxicologists are concerned about the potential for its cumulative neurotoxicity. It has been shown in several studies that the same neurotoxic effects can be observed at low and high doses of acrylamide, with the low doses simply requiring longer exposures. This review is focused on the neurotoxicity of acrylamide and its possible outcomes.

http://www.ncbi.nlm.nih.gov/pubmed/23541332

“According to our results, Acrylamide can affect sperm parameters as well as sperm chromatin condensation and DNA integrity in mice.”

Iranian Journal Of Reproductive Medicine • May 2014

Effects of acrylamide on sperm parameters, chromatin quality, and the level of blood testosterone in mice

Author information

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Abstract

BACKGROUND

Acrylamide (AA) is an important industrial chemical primarily. AA is also found in carbohydrate-rich foods that are prepared at high temperatures, such as French fries and potato chips. It is demonstrated that AA is a carcinogen and reproductive toxin and has ability to induce sperm damage.

OBJECTIVE

The aim of this study was to observe the effects of AA on sperm parameters and evaluation of sperm chromatin quality and testosterone hormone in mice.

MATERIALS AND METHODS

Totally, 16 adult male mice were divided into two groups. Mice of group A fed on basal diet; group B received basal diet and AA (10 mg/kg, water solution) for 35 days. The right cauda epididymis was incised and then placed in Ham’s F10 culture media at 37(o)C for 15 min. Released spermatozoa were used to analyze count, motility, morphology and viability. To determine the sperm DNA integrity and chromatin condensation, the cytochemical techniques including Aniline blue, Acridine orange and Chromomycin A3 staining were used.

RESULTS

AA-treated mice had poor parameters in comparison with control animals. In sperm chromatin assessments, except TB ($p=0.16$), significant differences were found in all of the tests between two groups. It was also seen a significant decrease in concentration of blood testosterone in AA-treated animals when compared to controls ($p<0.001$).

CONCLUSION

According to our results, AA can affect sperm parameters as well as sperm chromatin condensation and DNA integrity in mice. These abnormalities may be related to the reduction in blood testosterone.

Full Text with Graphs, Charts and 34 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC409465

“Subchronic exposure to acrylamide could affect the normal development of sperm, cause changes of the activity of some enzymes in the testis and significantly influence hindlimb motor coordination. Acrylamide directly damages Leydig cells and affects the endocrine function of the testis.”

Zhonghua Nan Ke Xue • May 2008

Subchronic exposure to acrylamide affects reproduction and testis endocrine function of rats

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Abstract

OBJECTIVE
To explore the effect of subchronic exposure to acrylamide on the reproduction and testis endocrine function of rats.

METHODS
Forty healthy adult male SD rats were randomly divided into 4 groups of equal number, exposed to acrylamide at the dose of 0, 4, 10 and 18 mg/(kg x d) respectively for 9 weeks, and then subjected to the determination of the hindlimb landing foot splay, sperm vitality and morphology, the activities of acid phosphatase (ACP) and alkaline phosphatase (ALP) in the testis homogenate, and the levels of testosterone (T) and estradiol (E2) in the serum and testis homogenate. Based on the primary Leydig cell culture models exposed to acrylamide of 0, 0.1, 0.75, 4 and 8 mmol/L, the activity of Leydig cells was measured by the CCK-8 method.

RESULTS
Following acrylamide exposure, the hindlimb landing foot splay increased markedly with dose increase ($P < 0.01$). The rates of sperm vitality were (6.86 +/- 5.46)%, (65.43 +/- 5.16)%, (60.86 +/- 4.26)% and (46.86 +/- 2.73)% in the exposed groups, significantly lower than in the control ($P < 0.01$); the rates of abnormal sperm were (39.00 +/- 10.95)%, (35.43 +/- 7.54)%, (45.71 +/- 13.28)% and (56.71 +/- 17.01)%, significantly increased in the 10 and 18 mg/(kg x d) groups ($P < 0.05$); ACP activities were (82.93 +/- 11.05), (73.52 +/- 8.77), (77.67 +/- 3.04) and (68.56 +/- 3.09) U/g prot, showing a decreasing tendency, while ALP activities were (0.96 +/- 0.15), (1.07 +/- 0.22), (1.12 +/- 0.22) and (0.74 +/- 0.10) U/g prot, displaying a tendency of first increasing and then decreasing. Both ACP and ALP activities were inhibited significantly in the 18 mg/(kg x d) group as compared with the control ($P < 0.05$). A marked reduction was noted in T levels in the serum, (13.44 +/- 4.76), (7.69 +/- 3.84), (5.23 +/- 1.42) and (1.36 +/- 0.86) ng/ml, as well as in the testis homogenate, (4.95 +/- 1.64), (3.01 +/- 0.76), (2.44 +/- 0.91) and (0.85 +/- 0.49) ng/mg prot, ($P < 0.01$), but no significant changes were observed in 17beta-E2 levels. After 24 hours exposure to acrylamide, the optical densities were 0.82 +/- 0.06, 0.56 +/- 0.07, 0.44 +/- 0.06, 0.26 +/- 0.03 and 0.45 +/- 0.21, showing an evident inhibition of the activity of Leydig cells at the dose of 0.1, 0.75, 4 and 8 mmol/L ($P < 0.01$).

CONCLUSION
Subchronic exposure to acrylamide could affect the normal development of sperm, cause changes of the activity of some enzymes in the testis and significantly influence hindlimb motor coordination. Acrylamide directly damages Leydig cells and affects the endocrine function of the testis.

http://www.ncbi.nlm.nih.gov/pubmed/18572857

Journal Of Agriculture And Food Chemistry • August 2008

Acrylamide carcinogenicity

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Abstract

"The induction of cancer by chemicals is a multiple-stage process. Acrylamide is carcinogenic to experimental mice and rats, causing tumors at multiple organ sites in both species when given in drinking water or by other means. In mice, acrylamide increased the incidence and multiplicity of lung tumors and skin tumors. In two bioassays in rats, acrylamide administered in drinking water consistently induced mesotheliomas of the testes, thyroid tumors, and mammary gland tumors. In addition, brain tumors appeared to be increased. In one of the rat bioassays, pituitary tumors, pheochromocytomas, uterine tumors, and pituitary tumors were noted. The conversion of acrylamide metabolically to the reactive, mutagenic, and genotoxic product, glycidamide, can occur in both rodent and humans. Glycidamide and frequently acrylamide have been positive for mutagenicity and DNA reactivity in a number of in vitro and in vivo assays. The effects of chronic exposure of glycidamide to rodents have not been reported. Epidemiologic studies of workers for possible health effects from exposures to acrylamide have not shown a consistent increase in cancer risk. Although an increase in the risk for pancreatic cancer (almost double) was seen in highly exposed workers, no exposure response relationship could be determined. The mode of action remains unclear for acrylamide-induced rodent carcinogenicity, but support for a genotoxic mechanism based on in vitro and in vivo DNA reactivity assays cannot be ruled out. In addition, the pattern of tumor formation in the rat following chronic exposure supports a genotoxic mode of action but also suggests a potential role of endocrine modification."

http://www.ncbi.nlm.nih.gov/pubmed/18624430

“Acrylamide has toxic effects on seminiferous tubules and decreases the production of sperm in male rats.”

Zhonghua Nan Ke Xue • June 2007

Oral acrylamide affects the development and reproductive performance of male rats

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Abstract

OBJECTIVE

The content of acrylamide increases remarkably in fried, baked and heat-processed starchy foods. The present experiment was aimed at investigating the toxicity of acrylamide on the reproductive system in male rats.

METHODS

Thirty weaned 21-day-old SD male rats were randomly allotted into three groups of 10 each. Group I and Group II were fed on water solutions containing acrylamide 5 mg/kg/d and 10 mg/kg/d for eight consecutive weeks, while the third group on fresh water only as the control. The body weight, viscera weights and testicle and epididymis tissues were detected at the fourth and eighth week respectively. In the end of the experiment, the sperm reserve and morphology in the cauda of the epididymis were examined.

RESULTS

The growth of the rats treated with acrylamide was retarded ($P < 0.05$). The weights of the testis and epididymis and the sperm concentration in the cauda of the epididymis of Group II were decreased significantly ($P < 0.05$) after acrylamide administration, while no significant change was observed in the sperm concentration of Group I ($P > 0.05$). Furthermore, histopathological lesions were presented in the testes of the treated rats, and the number of Leydig cells around the apoptosis seminiferous tubules increased significantly ($P < 0.05$).

CONCLUSION

Acrylamide has toxic effects on seminiferous tubules and decreases the production of sperm in male rats.

http://www.ncbi.nlm.nih.gov/pubmed/17615970

Food Additive Contaminants • July 2007

Acrylamide in cereal and cereal products: a review on progress in level reduction

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Abstract

“In March 2006, a joint workshop was organized by the European Commission and the Confederation of EU Food and Drink Industries (CIAA) to discuss current knowledge and achievements in the reduction of acrylamide levels. This paper focuses on the progress made with cereal products. At present, the reduction options available are applicable to a limited number of cereal products and are product-specific. The following are the most promising: * Adjustment of time and temperature during baking. * Extend fermentation times where feasible. * Substitution of ammonium bicarbonate with alternatives where feasible. * Avoid or minimise use of reducing sugars where possible. * Maintenance of uniform control of the colour and avoidance of very high baking temperature where possible. The most promising near-term technical solution is the use of asparaginase. This enzyme has the potential to achieve a 60-90% reduction for some products made from dough or batter, which can be held for a time. In the longer term, the optimisation of agronomy and plant breeding for wheat has the potential to reduce acrylamide in all foods on any scale, whether domestic or industrial. Importantly, nutritional and toxicological issues, other than acrylamide, must also be considered so as to ensure that the steps taken to reduce acrylamide levels do not have other adverse effects on diet.”

http://www.ncbi.nlm.nih.gov/pubmed/17687699

Asia Pacific Journal Of Clinical Nutrition • August 2007

Study on reduction of acrylamide in fried bread sticks by addition of antioxidant of bamboo leaves and extract of green tea

Author information

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Abstract

“This paper investigated the efficiency of antioxidant of bamboo leaves (AOB) and extract of green tea (EGT) on the reduction of acrylamide in fried bread sticks and summarized the optimal levels of two additives. Seven experimental groups including a control group were organized for both of additives. Fried bread sticks were made via traditional processing technology. The flour was mixed with different levels (0.002-4.9 g/kg flour) of AOB and EGT, respectively. The acrylamide level in fried bread sticks was determined by liquid chromatography tandem mass spectrometry (LC-MS/MS). The sensory evaluation was performed in double blind manner. Results showed that nearly 82.9% and 72.5% of acrylamide were reduced when the AOB and EGT addition levels were 1 and 0.1 g/kg, respectively. The elevated inhibitory effects of AOB and EGT on the acrylamide formation were achieved with an increase of additive levels unless the spiking levels of AOB and EGT were greater than 1 and 0.1 g/kg, respectively. Sensory evaluation results showed that the flavor and texture of fried bread sticks processed by AOB and EGT had no significant difference compared to normal food matrixes ($p>0.05$) when both AOB and EGT addition levels were no more than 1 g/kg. The present study indicated that both AOB and EGT could significantly reduce the acrylamide content generated in fried bread sticks and keep original flavor and crispness of fried bread sticks. This study could be regarded as an important contribution on the reduction of acrylamide by natural antioxidants.”

Full text, graphs, charts and 39 references

http://apjcn.nhri.org.tw/server/APJCN/16%20Suppl%201//131.pdf

“The results indicate that both AA and GA are genotoxic in mice.”

Environmental Molecular Mutagens • January 2006

Genotoxicity of acrylamide and its metabolite glycidamide administered in drinking water to male and female Big Blue mice

Author information

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Abstract

The recent discovery of acrylamide (AA), a probable human carcinogen, in a variety of fried and baked starchy foods has drawn attention to its genotoxicity and carcinogenicity. Evidence suggests that glycidamide (GA), the epoxide metabolite of AA, is responsible for the genotoxic effects of AA. To investigate the in vivo genotoxicity of AA, groups of male and female Big Blue (BB) mice were administered 0, 100, or 500 mg/l of AA or equimolar doses of GA, in drinking water, for 3-4 weeks. Micronucleated reticulocytes (MN-RETs) were assessed in peripheral blood within 24 hr of the last treatment, and lymphocyte Hprt and liver cII mutagenesis assays were conducted 21 days following the last treatment. Further, the types of cII mutations induced by AA and GA in the liver were determined by sequence analysis. The frequency of MN-RETs was increased 1.7-3.3-fold in males treated with the high doses of AA and GA (P < or = 0.05; control frequency = 0.28%). Both doses of AA and GA produced increased lymphocyte Hprt mutant frequencies (MFs), with the high doses producing responses 16-25-fold higher than that of the respective control (P < or = 0.01; control MFs = 1.5 +/- 0.3 x 10(-6) and 2.2 +/- 0.5 x 10(-6) in females and males, respectively). Also, the high doses of AA and GA produced significant 2-2.5-fold increases in liver cII MFs (P < or = 0.05; control MFs = 26.5 +/- 3.1 x 10(-6) and 28.4 +/- 4.5 x 10(-6)). Molecular analysis of the mutants indicated that AA and GA produced similar mutation spectra and that these spectra were significantly different from that of control mutants (P < or = 0.001). The predominant types of mutations in the liver cII gene from AA- and GA-treated mice were G:C-->T:A transversions and -1/+1 frameshifts in a homopolymeric run of Gs. The results indicate that both AA and GA are genotoxic in mice. The MFs and types of mutations induced by AA and GA in the liver are consistent with AA exerting its genotoxicity in BB mice via metabolism to GA.

http://www.ncbi.nlm.nih.gov/pubmed/15957192

Journal Of Veterinary Science • June 2005

Genotoxicity and toxicological effects of acrylamide on reproductive system in male rats

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Abstract

"The toxicity of acrylamide was evaluated through mutagenicity of Salmonella, chromosome aberration of Chinese hamster lung fibroblasts, micronucleus formation in mice and reproductive toxicity in rats. Based on Ames test, acrylamide showed mutagenic potency for strains TA98 and TA100. Moreover, both chromosomal aberration assay and micronucleus assay indicated that acrylamide might have genotoxic potency; the chromosomal aberration frequencies were observed to be proportional to acrylamide concentrations of 5-50 mM, and acrylamide significantly increased micronuclei in peripheral blood cells of mice at doses of higher than 72.5 mg/kg. Male rats were treated with acrylamide at doses of 0, 5, 15, 30, 45, or 60 mg/kg/day for 5 consecutive days, and the toxicity of acrylamide was observed. In the group treated with the highest dose of acrylamide (60 mg/kg/day), the loss of body weight and reduced testis weight were observed. Also the epididymides weights were reduced significantly in all the groups treated with acrylamide. The number of sperms in cauda epididymidis decreased significantly in an acrylamide dose-dependent manner. Rats treated with 60 mg/kg/day of acrylamide showed several histopathological lesions in the seminiferous tubules. There were thickening and multiple layering of the tubular endothelium, and the formation of many multinucleated giant cells in seminiferous tubules. Taken together, acrylamide not only causes the genotoxicity of eukaryotic cells and mice but also shows the toxicological effects on reproductive system in male rats."

Full text PDF link at top of page with 39 references

http://www.vetsci.org/journal/view.html?uid=248&vmd=Full

Critical Reviews Of Food Science And Nutrition • May 2004

A review of acrylamide: an industry perspective on research, analysis, formation, and control

Author information
Taeymans D1, Wood J, Ashby P, Blank I, Studer A, Stadler RH,
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Abstract

"Acrylamide is a synthetic monomer with a wide scope of industrial applications, mainly as a precursor in the production of several polymers, such as polyacrylamide. The main uses of polyacrylamides are in water and wastewater treatment processes, pulp and paper processing, and mining and mineral processing. The announcement by the Swedish National Food Administration in April 2002 of the presence of acrylamide predominantly in heat-treated carbohydrate-rich foods sparked intensive investigations into acrylamide, encompassing the occurrence, chemistry, agricultural practices, and toxicology, in order to establish if there is a potential risk to human health from the presence of this contaminant in the human diet. The link of acrylamide in foods to the Maillard reaction and, in particular, to the amino acid asparagine has been a major step forward in elucidating the first feasible chemical route of formation during the preparation and processing of food. Other probably minor pathways have also been proposed, including acrolein and acrylic acid. This review addresses the analytical and mechanistic aspects of the acrylamide issue and summarizes the progress made to date by the European food industries in these key areas. Essentially, it presents experimental results generated under laboratory model conditions, as well as under actual food processing conditions covering different food categories, such as potatoes, biscuits, cereals, and coffee. Since acrylamide formation is closely linked to food composition, factors such as the presence of sugars and availability of free amino acids are also considered. Many new findings that contribute towards a better understanding of the formation and presence of acrylamide in foods are presented. Many national authorities across the world are assessing the dietary exposure of consumers to acrylamide, and scientific projects have commenced to gather new information about the toxicology of acrylamide. These are expected to provide new scientific knowledge that will help to clarify whether or not there is a risk to human health from the consumption of foods containing low amounts of acrylamide."

http://www.ncbi.nlm.nih.gov/pubmed/15540646

“... intoxication at either acrylamide dose-rate produced a terminalopathy, i.e. nerve terminal degeneration and swelling were present ... Exposure to the higher acrylamide dose-rate caused early onset (day 5), widespread nerve terminal degeneration in most of the major forebrain areas, e.g. cerebral cortex, thalamus, hypothalamus and basal ganglia. Our findings indicate that nerve terminals were selectively affected in forebrain areas ...”

Neurotoxicology • January 2003

Acrylamide neuropathy III. Spatiotemporal characteristics of nerve cell damage in forebrain

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Abstract

Previous studies of acrylamide (ACR) neuropathy in rat PNS [Toxicol. Appl. Pharmacol. (1998) 151:211-221] and in spinal cord, brainstem and cerebellum [NeuroToxicology (2002a) 23:397-414; NeuroToxicology (2002b) 23:415-429] have suggested that axon degeneration was not a primary effect and was, therefore, of unclear neurotoxicological significance. To conclude our studies of neurodegeneration in rat CNS during ACR neurotoxicity, a cupric silver stain method was used to define spatiotemporal characteristics of nerve cell body, dendrite, axon and terminal argyrophilia in forebrain regions and nuclei. Rats were exposed to ACR at a dose-rate of either 50 mg/kg per day (i.p.) or 21 mg/kg per day (p.o.) and at selected times brains were removed and processed for silver staining. Results show that intoxication at either ACR dose-rate produced a terminalopathy, i.e. nerve terminal degeneration and swelling were present in the absence of significant argyrophilic changes in neuronal cell bodies, dendrites or axons. Exposure to the higher ACR dose-rate caused early onset (day 5), widespread nerve terminal degeneration in most of the major forebrain areas, e.g. cerebral cortex, thalamus, hypothalamus and basal ganglia. At the lower dose-rate, nerve terminal degeneration in the forebrain developed early (day 7) but exhibited a relatively limited spatial distribution, i.e. anteroventral thalamic nucleus and the pars reticulata of the substantia nigra. Several hippocampal regions were affected at a later time point (day 28), i.e. CA1 field and subicular complex. At both dose-rates, argyrophilic changes in forebrain nerve terminals developed prior to the onset of significant gait abnormalities. Thus, in forebrain, ACR intoxication produced a pure terminalopathy that developed prior to the onset of significant neurological changes and progressed as a function of exposure. Neither dose-rate used in this study was associated with axon degeneration in any forebrain region. Our findings indicate that nerve terminals were selectively affected in forebrain areas and, therefore, might be primary sites of ACR action.

http://www.ncbi.nlm.nih.gov/pubmed/12564388

“... based on accumulating evidence, we have hypothesized that nerve terminals, and not axons, are the primary site of Acrylamide action ...”

Toxicology And Applied Pharmacology • May 2003

Acrylamide axonopathy revisited

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Abstract

Distal swelling and eventual degeneration of axons in the CNS and PNS have been considered to be the characteristic neuropathological features of acrylamide (ACR) neuropathy. These axonopathic changes have been the basis for classifying ACR neuropathy as a central-peripheral distal axonopathy and, accordingly, research over the past 30 years has focused on the primacy of axon damage and on deciphering underlying mechanisms. However, based on accumulating evidence, we have hypothesized that nerve terminals, and not axons, are the primary site of ACR action and that compromise of corresponding function is responsible for the autonomic, sensory, and motor defects that accompany ACR intoxication (NeuroToxicology 23 (2002) 43). In this paper, we provide a review of data from a recently completed comprehensive, longitudinal silver stain study of brain and spinal cord from rats intoxicated with ACR at two different daily dosing rates, i.e., 50 mg/kg/day, ip or 21 mg/kg/day, po. Results show that, regardless of dose-rate, ACR intoxication was associated with early, progressive nerve terminal degeneration in all CNS regions and with Purkinje cell injury in cerebellum. At the lower dose-rate, initial nerve terminal argyrophilia was followed by abundant retrograde axon degeneration in white matter tracts of spinal cord, brain stem, and cerebellum. The results support and extend our nerve terminal hypothesis and suggest that Purkinje cell damage also plays a role in ACR neurotoxicity. Substantial evidence now indicates that axon degeneration is a secondary effect and is, therefore, not pathophysiologically significant. These findings have important implications for future mechanistic research, classification schemes, and assessment of neurotoxicity risk.

http://www.ncbi.nlm.nih.gov/pubmed/12729714

Journal Of Agriculture And Food Chemistry • July 2003

Chemistry, biochemistry, and safety of acrylamide. A review

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Abstract

“Acrylamide (CH2=CH-CONH2), an industrially produced alpha,beta-unsaturated (conjugated) reactive molecule, is used worldwide to synthesize polyacrylamide. Polyacrylamide has found numerous applications as a soil conditioner, in wastewater treatment, in the cosmetic, paper, and textile industries, and in the laboratory as a solid support for the separation of proteins by electrophoresis. Because of the potential of exposure to acrylamide, effects of acrylamide in cells, tissues, animals, and humans have been extensively studied. Reports that acrylamide is present in foods formed during their processing under conditions that also induce the formation of Maillard browning products heightened interest in the chemistry, biochemistry, and safety of this vinyl compound. Because exposure of humans to acrylamide can come from both external sources and the diet, a need exists to develop a better understanding of its formation and distribution in food and its role in human health. To contribute to this effort, this integrated review presents data on the chemistry, analysis, metabolism, pharmacology, and toxicology of acrylamide. Specifically covered are the following aspects: nonfood and food sources; exposure from the environment and the diet; mechanism of formation in food from asparagine and glucose; asparagine-asparaginase relationships; Maillard browning-acrylamide relationships; quenching of protein fluorescence; biological alkylation of amino acids, peptides, proteins, and DNA by acrylamide and its epoxide metabolite glycidamide; risk assessment; neurotoxicity, reproductive toxicity, and carcinogenicity; protection against adverse effects; and possible approaches to reducing levels in food. Further research needs in each of these areas are suggested. Neurotoxicity appears to be the only documented effect of acrylamide in human epidemiological studies; reproductive toxicity, genotoxicity/clastogenicity, and carcinogenicity are potential human health risks on the basis of only animal studies. A better understanding of the chemistry and biology of pure acrylamide in general and its impact in a food matrix in particular can lead to the development of improved food processes to decrease the acrylamide content of the diet.”

http://www.ncbi.nlm.nih.gov/pubmed/14705871

“... Acrylamide has also been shown to produce early nerve terminal degeneration of somatosensory, somatomotor and autonomic nerve fibers under a variety of dosing conditions. Recent research from our laboratory has demonstrated that terminal degeneration precedes axonopathy during low-dose subchronic induction of neurotoxicity and occurs in the absence of axonopathy during higher-dose subacute intoxication ...”

Neurotoxicology • May 2002

Nerve terminals as the primary site of acrylamide action: a hypothesis

Author information

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Abstract

Acrylamide (ACR) is considered to be prototypical among chemicals that cause a central-peripheral distal axonopathy. Multifocal neurofilamentous swellings and eventual degeneration of distal axon regions in the CNS and PNS have been traditionally considered the hallmark morphological features of this axonopathy. However, ACR has also been shown to produce early nerve terminal degeneration of somatosensory, somatomotor and autonomic nerve fibers under a variety of dosing conditions. Recent research from our laboratory has demonstrated that terminal degeneration precedes axonopathy during low-dose subchronic induction of neurotoxicity and occurs in the absence of axonopathy during higher-dose subacute intoxication. This relationship suggests that nerve terminal degeneration, and not axonopathy, is the primary or most important pathophysiologic lesion produced by ACR. In this hypothesis paper, we review evidence suggesting that nerve terminal degeneration is the hallmark lesion of ACR neurotoxicity, and we propose that this effect is mediated by the direct actions of ACR at nerve terminal sites. ACR is an electrophile and, therefore, sulfhydryl groups on presynaptic proteins represent rational molecular targets. Several presynaptic thiol-containing proteins (e.g. SNAP-25, NSF) are critically involved in formation of SNARE (soluble N-ethylmaleimide (NEM)-sensitive fusion protein receptor) complexes that mediate membrane fusion processes such as exocytosis and turnover of plasmalemmal proteins and other constituents. We hypothesize that ACR adduction of SNARE proteins disrupts assembly of fusion core complexes and thereby interferes with neurotransmission and presynaptic membrane turnover. General retardation of membrane turnover and accumulation of unincorporated materials could result in nerve terminal swelling and degeneration. A similar mechanism involving the long-term consequences of defective SNARE-based turnover of Na+/K(+)-ATPase and other axolemmal constituents might explain subchronic induction of axon degeneration. The ACR literature occupies a prominent position in neurotoxicology and has significantly influenced development of mechanistic hypotheses and classification schemes for neurotoxicants. Our proposal suggests a reevaluation of current classification schemes and mechanistic hypotheses that regard ACR axonopathy as a primary lesion.

http://www.ncbi.nlm.nih.gov/pubmed/12164547

“Consumption habits indicate that the acrylamide levels in the studied heated foods could lead to a daily intake of a few tens of micrograms.”

Journal Of Agriculture And Food Chemistry • August 2002

Analysis of acrylamide, a carcinogen formed in heated foodstuffs

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Abstract

Reaction products (adducts) of acrylamide with N termini of hemoglobin (Hb) are regularly observed in persons without known exposure. The average Hb adduct level measured in Swedish adults is preliminarily estimated to correspond to a daily intake approaching 100 microg of acrylamide. Because this uptake rate could be associated with a considerable cancer risk, it was considered important to identify its origin. It was hypothesized that acrylamide was formed at elevated temperatures in cooking, which was indicated in earlier studies of rats fed fried animal feed. This paper reports the analysis of acrylamide formed during heating of different human foodstuffs. Acrylamide levels in foodstuffs were analyzed by an improved gas chromatographic-mass spectrometric (GC-MS) method after bromination of acrylamide and by a new method for measurement of the underivatized acrylamide by liquid chromatography-mass spectrometry (LC-MS), using the MS/MS mode. For both methods the reproducibility, given as coefficient of variation, was approximately 5%, and the recovery close to 100%. For the GC-MS method the achieved detection level of acrylamide was 5 microg/kg and for the LC-MS/MS method, 10 microg/kg. The analytic values obtained with the LC-MS/MS method were 0.99 (0.95-1.04; 95% confidence interval) of the GC-MS values. The LC-MS/MS method is simpler and preferable for most routine analyses. Taken together, the various analytic data should be considered as proof of the identity of acrylamide. Studies with laboratory-heated foods revealed a temperature dependence of acrylamide formation. Moderate levels of acrylamide (5-50 microg/kg) were measured in heated protein-rich foods and higher contents (150-4000 microg/kg) in carbohydrate-rich foods, such as potato, beetroot, and also certain heated commercial potato products and crispbread. Acrylamide could not be detected in unheated control or boiled foods (<5 microg/kg). Consumption habits indicate that the acrylamide levels in the studied heated foods could lead to a daily intake of a few tens of micrograms.

http://www.ncbi.nlm.nih.gov/pubmed/12166997

“Thus, regardless of dose-rate, Acrylamide intoxication produced early, progressive nerve terminal degeneration. These data suggest that nerve terminals are a primary site of acrylamide action and that expression of axonopathy is restricted to subchronic dosing-rates.”

Neurotoxicology • September 2002

Acrylamide neuropathy II. Spatiotemporal characteristics of nerve cell damage in brainstem and spinal cord

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Abstract

Previous studies of acrylamide (ACR) neuropathy in rat PNS [Toxicol. Appl. Pharmacol. 151 (1998) 211] and cerebellum [Neurotoxicology, 2002a] have suggested that axon degeneration was not a primary effect and was, therefore, of unclear neurotoxicological significance. To continue morphological examination of ACR neurotoxicity in CNS, a cupric silver stain method was used to define spatiotemporal characteristics of nerve cell body, dendrite, axon and terminal degeneration in brainstem and spinal cord. Rats were exposed to ACR at a dose-rate of either 50 mg/kg per day (i.p.) or 21 mg/kg per day (p.o.), and at selected times brains and spinal cord were removed and processed for silver staining. Results show that intoxication at the higher ACR dose-rate produced a nearly pure terminalopathy in brainstem and spinal cord regions, ie. widespread nerve terminal degeneration and swelling were present in the absence of significant argyrophilic changes in neuronal cell bodies, dendrites or axons. Exposure to the lower ACR dose-rate caused initial nerve terminal argyrophilia in selected brainstem and spinal cord regions. As intoxication continued, axon degeneration developed in white matter of these CNS areas. At both dose-rates, argyrophilic changes in brainstem nerve terminals developed prior to the onset of significant gait abnormalities. In contrast, during exposure to the lower ACR dose-rate the appearance of axon degeneration in either brainstem or spinal cord was relatively delayed with respect to changes in gait. Thus, regardless of dose-rate, ACR intoxication produced early, progressive nerve terminal degeneration. Axon degeneration occurred primarily during exposure to the lower ACR dose-rate and developed after the appearance of terminal degeneration and neurotoxicity. Spatiotemporal analysis suggested that degeneration began at the nerve terminal and then moved as a function of time in a somal direction along the corresponding axon. These data suggest that nerve terminals are a primary site of ACR action and that expression of axonopathy is restricted to subchronic dosing-rates.

http://www.ncbi.nlm.nih.gov/pubmed/12387367

“Intoxication at the lower ACR dose-rate produced simultaneous (day 14) dendrite, axon and nerve terminal argyrophilia and no somatic Purkinje cell degeneration. The spatiotemporal pattern of dendrite, axon and nerve terminal loss induced by both ACR dose-rates is consistent with Purkinje cell injury. Injured neurons are likely to be incapable of maintaining distal processes and, therefore, axon degeneration in the cerebellum is a component of a “dying-back” process of neuronal injury.”

Neurotoxicology • September 2002

Acrylamide neuropathy. I. Spatiotemporal characteristics of nerve cell damage in rat cerebellum

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Abstract

Based on evidence from morphometric studies of PNS, we suggested that acrylamide (ACR)-induced distal axon degeneration was a secondary effect related to duration of exposure [Toxicol. Appl. Pharmacol. 151 (1998) 211]. To test this hypothesis in CNS, the cupric-silver stain method of de Olmos was used to define spatiotemporal characteristics of nerve somal, dendritic, axonal and terminal degeneration in rat cerebellum. Rats were exposed to ACR at either 50 mg/kg per day (i.p.) or 21 mg/kg per day (p.o.) and at selected times (i.p. = 5, 8 and 11 days; p.o. = 7, 14, 21, 28 and 38 days) brains were removed and processed for silver staining. Results demonstrate that intoxication at the higher ACR dose-rate produced early (day 5) and progressive degeneration of Purkinje cell dendrites in cerebellar cortex. Nerve terminal degeneration occurred concurrently with somatodendritic argyrophilia in cerebellar and brainstem nuclei that receive afferent input from Purkinje neurons. Relatively delayed (day 8), abundant axon degeneration was present in cerebellar white matter but not in cortical layers or in tracts carrying afferent fibers (cerebellar peduncles) from other brain nuclei. Axon argyrophilia coincided with the appearance of perikaryal degeneration, which was selective for Purkinje cells since silver impregnation of other cerebellar neurons was not evident in the different cortical layers or cerebellar nuclei. Intoxication at the lower ACR dose-rate produced simultaneous (day 14) dendrite, axon and nerve terminal argyrophilia and no somatic Purkinje cell degeneration. The spatiotemporal pattern of dendrite, axon and nerve terminal loss induced by both ACR dose-rates is consistent with Purkinje cell injury. Injured neurons are likely to be incapable of maintaining distal processes and, therefore, axon degeneration in the cerebellum is a component of a “dying-back” process of neuronal injury. Because cerebellar coordination of somatomotor activity is mediated solely through efferent projections of the Purkinje cell, injury to this neuron might contribute significantly to gait abnormalities that characterize ACR neurotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/12387366

Chemical Research In Toxicology • June 2000

Acrylamide: a cooking carcinogen?

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Abstract

“Exposure to acrylamide (AA) has been monitored by mass spectrometric detection of the adduct, N-(2-carbamoylethyl)valine (CEV), to the N-termini of hemoglobin (Hb), according to the N-alkyl Edman method. In these studies, a conspicuous background level, about 40 pmol/g of globin, of apparently the same adduct was regularly observed in Hb from persons without known exposure to AA. For testing of the hypothesis that this adduct originates from AA formed in cooking, rats were fed fried animal standard diet for 1 or 2 months. These animals exhibited a strong increase of the level of the studied Hb adduct, compared to control rats fed unfried diet. By gas chromatography/tandem mass spectrometry, the identity with CEV was confirmed by the concordance of the product ion spectrum of the studied adduct with that of a verified standard and by interpretation of the fragment ions. Further support of the chemical structure, at the same time pinpointing AA as the causative reactive factor, was obtained through the demonstration that AA is formed in the heating of the feed and that the level of AA in the fried feed is compatible with the measured levels of the CEV adduct. The raised CEV adduct levels observed in experimental animals are of a magnitude that is similar to the background level in nonsmoking humans. These data render it likely that cooking of food is a major source of the background dose of AA also in humans. An evaluation of cancer tests of AA and available data for its metabolism leads to the estimation that the background dose of AA is associated with a considerable cancer risk.”

http://www.ncbi.nlm.nih.gov/pubmed/10858325

“These results indicate that the toxicities of acrylamide and glycidamide differ and suggest that acrylamide itself may be primarily responsible for its peripheral neurotoxicity.”

Toxicology • April 1995

Evaluation of the neurotoxicity of glycidamide, an epoxide metabolite of acrylamide: behavioral, neurochemical and morphological studies

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Abstract

Acrylamide is an important chemical used in the synthesis of polyacrylamides, which have a wide variety of industrial applications. The principal toxic effect of acrylamide, both in animals and in humans, is neurotoxicity. Peripheral nervous system effects are most prominent, but central nervous system effects have also been reported. Acrylamide is metabolized to the epoxide glycidamide, whose adducts to hemoglobin and to DNA have been identified in animals and humans. This metabolite may be involved in the reproductive and carcinogenic effects of acrylamide. In the present study we investigated whether glycidamide would exert neurotoxic effects similar to those caused by its parent compound. Male rats were injected i.p. with acrylamide (25 or 50 mg/kg) or glycidamide (50 or 100 mg/kg) daily for 8 days. Reduced weight gain was evident in animals exposed to glycidamide or to the higher dose of acrylamide. Both compounds induced lethargy and ataxia, but the posture of glycidamide-treated rats differed from that of animals treated with acrylamide. At the high doses, both compounds significantly affected rats' behavior in the rotarod test; on the other hand, only acrylamide was effective in the hindlimb splay test. Acrylamide inhibited activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in sciatic and tibial nerves, as well as in brain. Glycidamide inhibited GAPDH activity only in brain and activity of creatine kinase in both peripheral and central tissues. Acrylamide also caused profound urinary retention and distended bladders, while the effects of glycidamide were minimal. Morphological abnormalities were seen in sciatic nerves and dorsal root ganglion cells of rats treated with acrylamide (50 mg/kg x 12), but not in rats exposed to glycidamide (100 mg/kg x 11). These results indicate that the toxicities of acrylamide and glycidamide differ and suggest that acrylamide itself may be primarily responsible for its peripheral neurotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/7740544

“It is now reported that acrylamide is absorbed through the skin of male mice, reaches the germ cells, and induces chromosomal damage. The magnitude of genetic damage appears to be proportional to the dose administered topically.”

Fundamentals Of Applied Toxicology • February 1992

Acrylamide:
dermal exposure produces genetic damage in male mouse germ cells

Author information

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Abstract

Acrylamide is used extensively in sewage and wastewater treatment plants, in the paper and pulp industry, in treatment of potable water, and in research laboratories for chromatography, electrophoresis, and electron microscopy. Dermal contact is a major route of human exposure. It has been shown that acrylamide is highly effective in breaking chromosomes of germ cells of male mice and rats when administered intraperitoneally or orally, resulting both in the early death of conceptuses and in the transmission of reciprocal translocations to live-born progeny. It is now reported that acrylamide is absorbed through the skin of male mice, reaches the germ cells, and induces chromosomal damage. The magnitude of genetic damage appears to be proportional to the dose administered topically.

http://www.ncbi.nlm.nih.gov/pubmed/1601219

CHAPTER EIGHT

Potassium Bromate • KBr03

The Peer Review

Potassium bromate (KBrO3), is a flour "improver" that strengthens dough and allows for greater oven spring and higher rising in the oven. Potassium bromate, commonly referred to as simply "bromate" is a slow-acting oxidizer, contributing its functionality through out the mixing, fermentation and proofing stages, with important residual action during the early stages of baking.

Azodicarbonamide (ADA), potassium and calciumiodate, and calciumperoxide are rapid-acting oxidizers, while ascorbic acid (vitamin C) works at intermediate rates, but all release their activity in mixing and proofing. Bromate, when applied within the prescribed limits (15-30ppm), is completely used up during the bake leaving no trace in the finished product. However, if too much is used, or the bread is not baked long enough or at a high enough temperature, then a residual amount will remain.

The primary concern regarding the use of bromates in baking is its demonstrated link to cancer in laboratory animals and now, based on newer peer review, in humans. It was first found to induce tumors in rats in 1982. However, since 1991, instead of banning bromate outright the FDA, with somewhat limited success, has merely encouraged bakers to voluntarily stop using it.

Bromates have been banned in numerous countries, including the United Kingdom in 1990 and Canada in 1994, Japan and a dozen more countries. In addition, in 1991, California declared bromate a carcinogen under the state's Proposition 65. As such, baked goods sold in California would have to bear a store level cancer warning if they contained more than a certain level of bromate. As a result, most California bakers have switched to bromate-free processes.

The only changes that most bakers find they need to make are slightly longer mixing times. Bromate, being an oxidizer, rapidly strengthens the dough in the mixer bowl thus reducing mixing times. Doughs made from unbromated flours will require slightly more mixing to achieve the same strength. As you do not want to increase the final temperature of your dough through this additional mixing you must lower your initial water temperature. Those changes should be all that is required to make the switch. It's a simple fix and a proven poison.

Some bakers find that they don't have as much fermentation tolerance using un-bromated flour. There are two fixes for this. One is to use preferments in your dough. This increases the acidity of your dough giving it more tolerance for longer proof times and overnight retarding. If this doesn't fit your production requirements then you can consider using ascorbic acid (Vitamin C). Ascorbic acid is a slow acting oxidizer so you won't get much benefit in the mixer but your dough will have more tolerance to overnight retarding.

Given all of the health risks involved with the use of bromates, as you can plainly see from the peer review in this chapter, we should have never used potassium bromate in the first place. Quality organic ingredients produce great health and robust immune systems. Avoid this additive and all additives at all costs.

Potassium bromate is classified as a category 2B carcinogen (possibly carcinogenic to humans) by the International Agency for Research on Cancer (IARC).

Japanese baked goods manufacturers stopped using potassium bromate voluntarily in 1980; however, Yamazaki Baking resumed its use in 2005, claiming they had new production methods to reduce the amount of the chemical which remained in the final product. Peer reviewed testing disagrees in that there is no safe level of potassium bromate. It's a human, insect and animal poison as pointed out in the reports and studies here.

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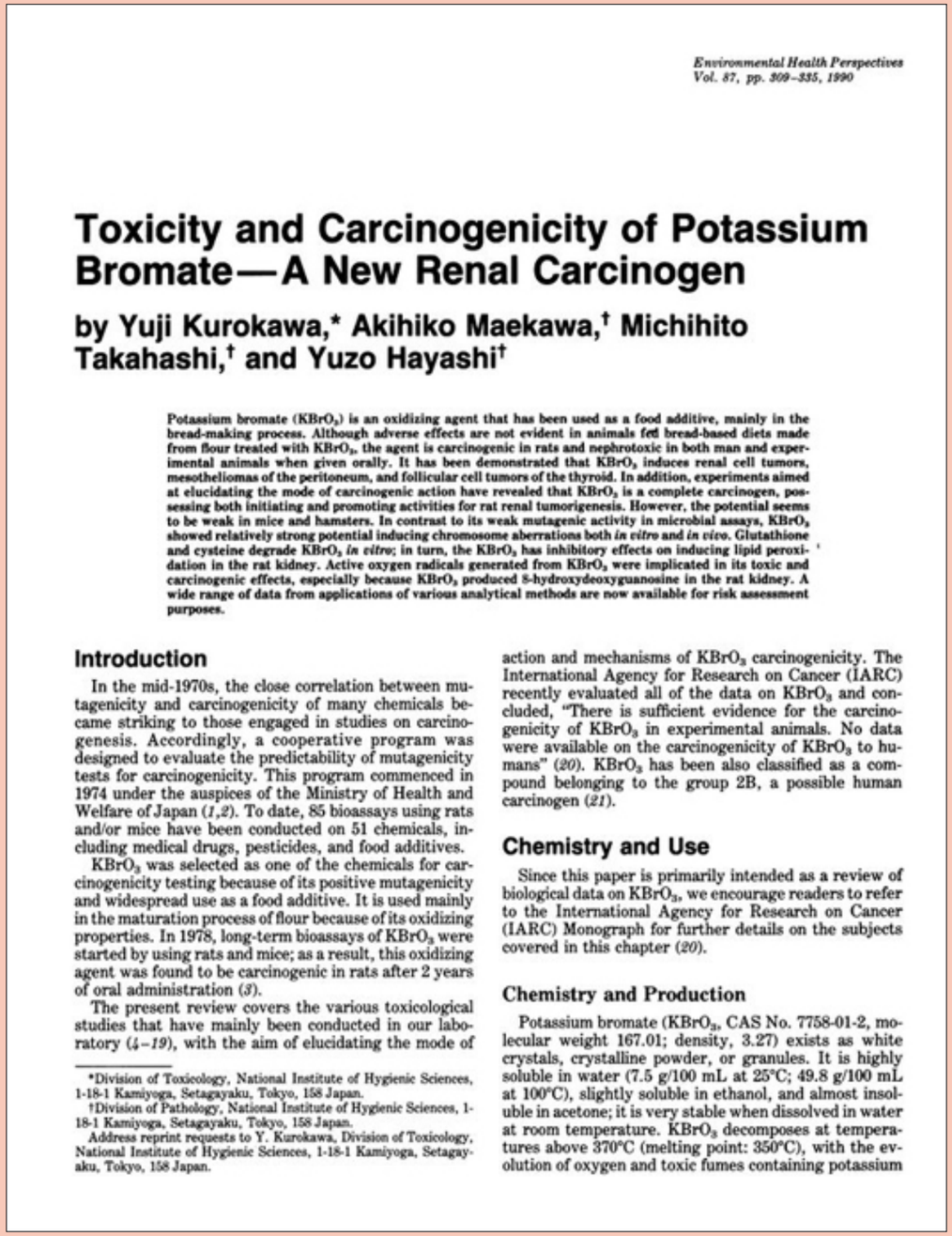
POTASSIUM BROMATE IS TOXIC AND CARCINOGENIC

And We Knew More Than 25 Years Ago

More than 25 years ago, in 1990 in volume 87, pages 309 through 335, peer reviewed and successfully published in the prestigious and respected Journal Environmental Health Perspectives, still published today, Yuji Kurokawa wrote that,

"the present review covers the various toxicological studies that have mainly been conducted in our laboratory (4-19), with the aim of elucidating the mode of actions and mechanisms of KBrO3 carcinogenicity. The International Agency for Resarch on Cancer (IARC) recently evaluated all of the data on KBrO3 and concluded, "There is sufficient evidence for the carcinogenicity of KBrO3 in experimental animals. No data were available on the carcinogenicity of KBrO3 to humans". KBrO3 has been also classified as a compound belonging to the group 2B, a possible human carcinogen"



Environmental Health Perspectives
Vol. 87, pp. 309–335, 1990

Toxicity and Carcinogenicity of Potassium Bromate—A New Renal Carcinogen

by Yuji Kurokawa,* Akihiko Maekawa,† Michihito Takahashi,† and Yuzo Hayashi†

Potassium bromate ($KBrO_3$) is an oxidizing agent that has been used as a food additive, mainly in the bread-making process. Although adverse effects are not evident in animals fed bread-based diets made from flour treated with $KBrO_3$, the agent is carcinogenic in rats and nephrotoxic in both man and experimental animals when given orally. It has been demonstrated that $KBrO_3$ induces renal cell tumors, mesotheliomas of the peritoneum, and follicular cell tumors of the thyroid. In addition, experiments aimed at elucidating the mode of carcinogenic action have revealed that $KBrO_3$ is a complete carcinogen, possessing both initiating and promoting activities for rat renal tumorigenesis. However, the potential seems to be weak in mice and hamsters. In contrast to its weak mutagenic activity in microbial assays, $KBrO_3$ showed relatively strong potential inducing chromosome aberrations both *in vitro* and *in vivo*. Glutathione and cysteine degrade $KBrO_3$ *in vitro*; in turn, the $KBrO_3$ has inhibitory effects on inducing lipid peroxidation in the rat kidney. Active oxygen radicals generated from $KBrO_3$ were implicated in its toxic and carcinogenic effects, especially because $KBrO_3$ produced 8-hydroxydeoxyguanosine in the rat kidney. A wide range of data from applications of various analytical methods are now available for risk assessment purposes.

Introduction

In the mid-1970s, the close correlation between mutagenicity and carcinogenicity of many chemicals became striking to those engaged in studies on carcinogenesis. Accordingly, a cooperative program was designed to evaluate the predictability of mutagenicity tests for carcinogenicity. This program commenced in 1974 under the auspices of the Ministry of Health and Welfare of Japan (*1,2*). To date, 85 bioassays using rats and/or mice have been conducted on 51 chemicals, including medical drugs, pesticides, and food additives.

$KBrO_3$ was selected as one of the chemicals for carcinogenicity testing because of its positive mutagenicity and widespread use as a food additive. It is used mainly in the maturation process of flour because of its oxidizing properties. In 1978, long-term bioassays of $KBrO_3$ were started by using rats and mice; as a result, this oxidizing agent was found to be carcinogenic in rats after 2 years of oral administration (*3*).

The present review covers the various toxicological studies that have mainly been conducted in our laboratory (*4–19*), with the aim of elucidating the mode of action and mechanisms of $KBrO_3$ carcinogenicity. The International Agency for Research on Cancer (IARC) recently evaluated all of the data on $KBrO_3$ and concluded, "There is sufficient evidence for the carcinogenicity of $KBrO_3$ in experimental animals. No data were available on the carcinogenicity of $KBrO_3$ to humans" (*20*). $KBrO_3$ has been also classified as a compound belonging to the group 2B, a possible human carcinogen (*21*).

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Chemistry and Use

Since this paper is primarily intended as a review of biological data on $KBrO_3$, we encourage readers to refer to the International Agency for Research on Cancer (IARC) Monograph for further details on the subjects covered in this chapter (*20*).

Chemistry and Production

Potassium bromate ($KBrO_3$, CAS No. 7758-01-2, molecular weight 167.01; density, 3.27) exists as white crystals, crystalline powder, or granules. It is highly soluble in water (7.5 g/100 mL at 25°C; 49.8 g/100 mL at 100°C), slightly soluble in ethanol, and almost insoluble in acetone; it is very stable when dissolved in water at room temperature. $KBrO_3$ decomposes at temperatures above 370°C (melting point: 350°C), with the evolution of oxygen and toxic fumes containing potassium

“Potassium bromate (KBrO3) is widely used as a food-additive and is a major water disinfection by-product. KBrO3 causes severe toxicity in humans and experimental animals. Bromate is considered a probable human carcinogen and a complete carcinogen in animals.”

Environmental Toxicology • March 2016

Protective effect of taurine against potassium bromate-induced hemoglobin oxidation, oxidative stress, and impairment of antioxidant defense system in blood

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Abstract

Potassium bromate (KBrO3) is widely used as a food-additive and is a major water disinfection by-product. KBrO3 causes severe toxicity in humans and experimental animals. Bromate is considered a probable human carcinogen and a complete carcinogen in animals. We have investigated the potential role of taurine in protecting against KBrO3 -induced oxidative stress in rat blood. Animals were given taurine for 5 days prior to KBrO3 and then sacrificed. Blood was collected and used to prepare hemolysates and plasma, which were then used for the analysis of several biochemical parameters. Administration of single oral dose of KBrO3 alone induced hepato- and nephro-toxicity as evident by elevated marker levels in plasma. Lipid peroxidation and protein oxidation were increased both in plasma and erythrocytes, suggesting the induction of oxidative stress. KBrO3 increased methemoglobin, nitric oxide, and hydrogen peroxide levels. It also altered the activities of the major antioxidant enzymes and lowered the antioxidant power of blood. Administration of taurine, prior to treatment with KBrO3, resulted in significant attenuation in all these parameters but the administration of taurine alone had no effect. These results show that taurine is effective in mitigating the oxidative insult induced in rat blood by KBrO3 .

http://www.ncbi.nlm.nih.gov/pubmed/25213677

PLoS One • March 2015

Chemoprotective effect of taurine on potassium bromate-induced DNA damage, DNA-protein cross-linking and oxidative stress in rat intestine

Author information

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Abstract

Potassium bromate (KBrO3) is widely used as a food additive and is a major water disinfection by-product. It induces multiple organ toxicity in humans and experimental animals and is a probable human carcinogen. The present study reports the protective effect of dietary antioxidant taurine on KBrO3-induced damage to the rat intestine. Animals were randomly divided into four groups: control, KBrO3 alone, taurine alone and taurine+ KBrO3. Administration of KBrO3 alone led to decrease in the activities of intestinal brush border membrane enzymes while those of antioxidant defence and carbohydrate metabolism were also severely altered. There was increase in DNA damage and DNA-protein cross-linking. Treatment with taurine, prior to administration of KBrO3, resulted in significant attenuation in all these parameters but the administration of taurine alone had no effect. Histological studies supported these biochemical results showing extensive intestinal damage in KBrO3-treated animals and greatly reduced tissue injury in the taurine+ KBrO3 group. These results show that taurine ameliorates bromate induced tissue toxicity and oxidative damage by improving the antioxidant defence, tissue integrity and energy metabolism. Taurine can, therefore, be potentially used as a therapeutic/protective agent against toxicity of KBrO3 and related compounds.

Full text with graphs, charts and 56 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4352022/

“Potassium bromate (KBrO3) is widely used as a food additive and is a major water disinfection by-product. It induces multiple organ toxicity in humans and experimental animals and is a probable human carcinogen.”

“The food additive potassium bromate (KBrO3) is known as a renal carcinogen and causes chromosomal aberrations in vitro without metabolic activation and in vivo in hematopoietic and renal cells.”

Mutatation Research, Genetic Toxicology & Environmental Mutagenesis • March 2015

Evaluation of repeated dose micronucleus assays of the liver and gastrointestinal tract using potassium bromate: a report of the collaborative study by CSGMT/JEMS.MMS

Author information

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Abstract

The food additive potassium bromate (KBrO3) is known as a renal carcinogen and causes chromosomal aberrations in vitro without metabolic activation and in vivo in hematopoietic and renal cells. As a part of a collaborative study by the Mammalian Mutagenicity Study group, which is a subgroup of the Japanese Environmental Mutagen Society, we administered KBrO3 to rats orally for 4, 14, and 28 days and examined the micronucleated (MNed) cell frequency in the liver, glandular stomach, colon, and bone marrow to confirm whether the genotoxic carcinogen targeting other than liver and gastrointestinal (GI) tract was detected by the repeated dose liver and GI tract micronucleus (MN) assays. In our study, animals treated with KBrO3 showed some signs of toxicity in the kidney and/or stomach. KBrO3 did not increase the frequency of MNed cells in the liver and colon in any of the repeated dose studies. However, KBrO3 increased the frequency of MNed cells in the glandular stomach and bone marrow. Additionally, the MNed cell frequency in the glandular stomach was not significantly affected by the difference in the length of the administration period. These results suggest that performing the MN assay using the glandular stomach, which is the first tissue to contact agents after oral ingestion, is useful for evaluating the genotoxic potential of chemicals and that the glandular stomach MN assay could be integrated into general toxicity studies.

http://www.ncbi.nlm.nih.gov/pubmed/24637080

“... Potassium Bromate influenced the albumin, creatinine, total cholesterol, triglycerides and glucose levels in male rats to various extents. A thorough analysis of the above tests clearly demonstrates that bromate has toxicity ...”

Regulatory Toxicology And Pharmacology • December 2015

Drinking water toxicity study of the environmental contaminant—Bromate

Author informationDongmei L1, Zhiwei W2, Qi Z3, Fuyi C4, Yujuan S5, Xiaodong L6.

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Abstract

Bromate is a byproduct of water disinfection that is produced when waters contain bromide treated with ozone. To investigate the level of the toxicity of bromate and find the most sensitive indicators in a short time, a series of toxicological assessments were conducted including the acute toxicity, cumulative toxicity, genetic toxicity and subacute toxicity of bromate (using Potassium Bromate to represent bromate). The LD50 of orally administered Potassium Bromate was 215 mg/kg in Wistar rats and 464 mg/kg in ICR mice. The cumulative toxicity of Potassium Bromate was not obvious. The Ames test, mouse bone marrow cell micronucleus test and mouse sperm abnormality test did not indicate mutagenicity. The results of the subacute study did not exhibit significant differences in most of the parameters, except the white blood cell count, which was significantly decreased in male rats. In addition, Potassium Bromate influenced the albumin, creatinine, total cholesterol, triglycerides and glucose levels in male rats to various extents. A thorough analysis of the above tests clearly demonstrates that bromate has toxicity, not obvious cumulative toxicity and the white blood cell count can be used as an indicator to reflect the toxicity of bromate and investigate bromate’s toxic mechanism.

http://www.ncbi.nlm.nih.gov/pubmed/26496820

“These results show that Potassium Bromate (KBrO3) induces oxidative stress in human erythrocytes through the generation of reactive oxygen species and alters the cellular antioxidant defense system.”

Environmental Toxicology • February 2014

Potassium bromate causes cell lysis and induces oxidative stress in human erythrocytes

Author information

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Abstract

In the present study, we have studied the effect of KBrO3 on human erythrocytes under in vitro conditions. Erythrocytes were isolated from the blood of healthy nonsmoking volunteers and incubated with different concentrations of KBrO3 at 37°C for 60 min. This resulted in marked hemolysis in a KBrO3 -concentration dependent manner. Lysates were prepared from KBrO3 -treated and control erythrocytes and assayed for various parameters. KBrO3 treatment caused significant increase in protein oxidation, lipid peroxidation, hydrogen peroxide levels, and decrease in total sulfhydryl content, which indicates induction of oxidative stress in human erythrocytes. Methemoglobin levels and methemoglobin reductase activity were significantly increased while the total antioxidant power of lysates was greatly reduced upon KBrO3 treatment. Intracellular production of reactive oxygen species increased in a dose dependent manner. Exposure of erythrocytes to KBrO3 also caused decrease in the activities of catalase, glutathione peroxidase, thioredoxin reductase, glucose 6-phosphate dehydrogenase and glutathione reductase whereas the activities of Cu-Zn superoxide dismutase and glutathione-S-transferase were increased. These results show that KBrO3 induces oxidative stress in human erythrocytes through the generation of reactive oxygen species and alters the cellular antioxidant defense system.

http://www.ncbi.nlm.nih.gov/pubmed/22012894

“Bacterial antibiotic resistance (BAR) in drinking water has become a global issue because of its risks on the public health. Our study indicated that mutagenic activities of the selected disinfection by-products could induce antibiotic resistance, even multi-drug resistance ...”

Environmental Science & Technology • July 2014

Exposure to mutagenic disinfection byproducts leads to increase of antibiotic resistance in Pseudomonas aeruginosa

Author information

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Abstract

Bacterial antibiotic resistance (BAR) in drinking water has become a global issue because of its risks on the public health. Usually, the antibiotic concentrations in drinking water are too low to select antibiotic resistant strains effectively, suggesting that factors other than antibiotics would contribute to the emergence of BAR. In the current study, the impacts of mutagenic disinfection byproducts (DBPs) on BAR were explored, using four typical DBPs: dibromoacetic acid, dichloroacetonitrile, potassium bromate, and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX). After exposure to DBPs, resistances to 10 individual antibiotics and multiple antibiotics were both raised by various levels, norfloxacin and polymycin B resistances were enhanced even greater than 10-fold compared with control. MX increased the resistance most observably in the selected DBPs, which was consistent with its mutagenic activity. The resistant mutants showed hereditary stability during 5-day culturing. The increase of BAR was caused by the mutagenic activities of DBPs, since mutation frequency declined by adding ROS scavenger. Mutagenesis was further confirmed by sequencing of the related genes. Our study indicated that mutagenic activities of the selected DBPs could induce antibiotic resistance, even multidrug resistance, which may partially explain the lack of agreement between BAR and antibiotic levels in drinking water.

http://www.ncbi.nlm.nih.gov/pubmed/24933271

“Collectively, these data show the novel finding that bromate-induced renal cell death is altered by inhibitors of epigenetic modifying enzymes and that bromate itself induces epigenetic changes in the p21 gene.”

Toxicological Sciences • October 2014

Epigenetic changes in p21 expression in renal cells after exposure to bromate

Author information

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Abstract

This study tested the hypothesis that bromate (KBrO3)-induced renal cell death is mediated by epigenetic mechanisms. Global DNA methylation, as assessed by 5-methylcytosine staining, was not changed in normal rat kidney cells treated with acute cytotoxic doses of KBrO3 (100 and 200 ppm), as compared with controls. However, KBrO3 treatment did increase p38, p53 and histone 2AX (H2AX) phosphorylation, and p21 expression. Treatment of cells with inhibitors of DNA methyltransferase (5-azacytidine or 5-Aza) and histone deacetylase (trichostatin A or TSA) in addition to KBrO3 increased cytotoxicity, as compared with cells exposed to KBrO3 alone. 5-Aza and TSA co-treatment did not alter p38 or p53 phosphorylation, but slightly decreased H2AX phosphorylation and significantly decreased p21 expression. We also assessed epigenetic changes in cells treated under sub-chronic conditions with environmentally relevant concentrations of KBrO3. Under these conditions (0-10ppm KBrO3 for up to 18 days), we detected no increases in cell death or DNA damage. In contrast, slight alterations were detected in the phosphorylation of H2AX, p38, and p53. Sub-chronic low-dose KBrO3 treatment also induced a biphasic response in p21 expression, with lower concentrations increasing expression, but higher concentrations decreasing expression. Methylation-specific PCR demonstrated that sub-chronic KBrO3 treatment altered the methylation of cytosine bases in the p21 gene, as compared with controls, correlating to alterations in p21 protein expression. Collectively, these data show the novel finding that KBrO3-induced renal cell death is altered by inhibitors of epigenetic modifying enzymes and that KBrO3 itself induces epigenetic changes in the p21 gene.

Full text with graphs, charts and 52 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4271043/

“Overall, the statistical analyses of DNA damage and mutations induced by KBrO(3) are consistent with a low-dose linear response and do not provide convincing evidence for the presence of a threshold.”

Environmental And Molecular Mutagenesis • January 2013

Dose-response analysis of bromate-induced DNA damage and mutagenicity is consistent with low-dose linear, nonthreshold processes

Author information

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Abstract

Mutagenic agents have long been inferred to act through low-dose linear, nonthreshold processes. However, there is debate about this assumption, with various studies interpreting datasets as showing thresholds for DNA damage and mutation. We have applied rigorous statistical analyses to investigate the shape of dose-response relationships for a series of in vitro and in vivo genotoxicity studies using potassium bromate (KBrO(3)), a water ozonation byproduct that is bioactivated to a reactive species causing oxidative damage to DNA. We analyzed studies of KBrO(3) genotoxicity where no-effect/threshold levels were reported as well as other representative datasets. In all cases, the data were consistent with low-dose linear models. In the majority of cases, the data were fit either by a linear (straight line) model or a model which was linear at low doses and showed a saturation-like downward curvature at high doses. Other datasets with apparent upward curvature were still adequately represented by models that were linear at low dose. Sensitivity analysis of datasets showing upward curvature revealed that both low-dose linear and nonlinear models provide adequate fits. Additionally, a simple biochemical model of selected key processes in bromate-induced DNA damage was developed and illustrated a situation where response for early primary events suggested an apparent threshold while downstream events were linear. Overall, the statistical analyses of DNA damage and mutations induced by KBrO(3) are consistent with a low-dose linear response and do not provide convincing evidence for the presence of a threshold.

http://www.ncbi.nlm.nih.gov/pubmed/23015362

“All the sampled bread had potassium bromate, in concentration above safe level for human consumption, therefore bread consumers and bakers are at risk of exposure to potassium bromate with health implications.”

International Journal Of Health & Nutrition • February 2013

Determination of Potassium Bromate content in Selected Bread Samples in Gwagwalada, Abuja-Nigeria

Author Information

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Abstract

Background

Potassium bromate (KBrO) is a nephrotoxic and carcinogenic substance used in food and cosmetics industry, and also found in drinking water as a by-product of disinfection. Despite the ban placed on the use of potassium bromate as bread-enhancer in Nigeria, it is commonly used by bakers to increase bread volume and texturem This study was aimed at determining the potassium bromate content of bread consumed in the Gwagwalada area council of Abuja, Nigeria, and evaluating the level of dietary exposure of this community to potassium bromate. The maximum concentration of potassium bromate allowed in bread by the US Food and Drug Agency (FDA) is 0.02µg/g (0.02mg/kg).

Methods

Quantitative determination of the level of potassium bromate in bread samples was done using spectrophotometric method that is based on the redox reaction between bromate and promethazine hydrochloride in an acidic medium. The absorbance of the product was read at 515nm. The qualitative test was performed directly on a portion of each bread sample using 2ml of 0.01M promethazine and 0.6ml of 12M hydrochloric acid. The change in colour of each bread sample to pink indicates the presence of potassium bromate.

Results

The 20 bread samples analyzed contain potassium bromate. The concentration of KBrO in the sampled bread is between 3.6µg/gm and 9.2µg/g. The quantity of KBrO in each bread sample correlates with the degree of pink colour obtained in the qualitative test.

Conclusion

All the sampled bread had potassium bromate, in concentration above safe level for human consumption, therefore bread consumers and bakers are at risk of exposure to potassium bromate with health implications. The need for continuous surveillance andm enforcement of the ban on use of potassium bromate in baking industry in Nigeria is recommended.

Full text with graphs, photos and charts and 16 references

http://www.academia.edu/4149521/Determination_of_Potassium_Bromate_content_in_Selected_Bread_Samples_in_Gwagwalada_Abuja_Nigeria

“Thus, a single oral dose of potassium bromate (KBrO3) exerts genotoxic effects in the intestine of rats, possibly through the mechanism of oxidative DNA damage.”

Chemosphere • May 2013

DNA damage and DNA-protein cross-linking induced in rat intestine by the water disinfection by-product potassium bromate

Author information

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Abstract

The genotoxic effects of potassium bromate (KBrO3), a food additive and water disinfection by-product, on the small intestine of rats are reported here. Adult male rats were given a single oral dose of KBrO3 (100 mg kg(-1) body weight) and sacrificed 12, 24, 48, 96 and 168 h after this treatment while control animals were not given KBrO3. Administration of KBrO3 caused a significant increase in DNA damage when analyzed by the comet assay which suggests the induction of DNA strand breaks. This was also shown by colorimetric assay of nucleotides formed upon DNA degradation. KBrO3 treatment also resulted in increased formation of DNA-protein cross-links in the intestine. The maximum changes in these parameters were 48 h after administration of KBrO3 after which recovery took place. Thus, a single oral dose of KBrO3 exerts genotoxic effects in the intestine of rats, possibly through the mechanism of oxidative DNA damage.

http://www.ncbi.nlm.nih.gov/pubmed/23391373

“A complex interaction between DNA mismatch repair and base excision repair, repair systems, that is, exposure dependent, also exists to determine cellular toxicity.”

Biomedical Research International • August 2013

The effect of Msh2 knockdown on toxicity induced by tert-butyl-hydroperoxide, potassium bromate, and hydrogen peroxide in base excision repair proficient and deficient cells

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Abstract

The DNA mismatch repair (MMR) and base excision repair (BER) systems are important determinants of cellular toxicity following exposure to agents that cause oxidative DNA damage. To examine the interactions between these different repair systems, we examined whether toxicity, induced by t-BOOH and KBrO3, differs in BER proficient (Mpg (+/+), Nth1 (+/+)) and deficient (Mpg (-/-), Nth1 (-/-)) mouse embryonic fibroblasts (MEFs) following Msh2 knockdown of between 79 and 88% using an shRNA expression vector. Msh2 knockdown in Nth1 (+/+) cells had no effect on t-BOOH and KBrO3 induced toxicity as assessed by an MTT assay; knockdown in Nth1 (-/-) cells resulted in increased resistance to t-BOOH and KBrO3, a result consistent with Nth1 removing oxidised pyrimidines. Msh2 knockdown in Mpg (+/+) cells had no effect on t-BOOH toxicity but increased resistance to KBrO3; in Mpg (-/-) cells, Msh2 knockdown increased cellular sensitivity to KBrO3 but increased resistance to t-BOOH, suggesting a role for Mpg in removing DNA damage induced by these agents. MSH2 dependent and independent pathways then determine cellular toxicity induced by oxidising agents. A complex interaction between MMR and BER repair systems, that is, exposure dependent, also exists to determine cellular toxicity.

Full text with graphs, charts and 35 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747367/

“Renal lipid peroxidation and protein carbonyls were increased while total sulfhydryl groups and reduced glutathione levels were decreased suggesting the induction of oxidative stress. The enzymes of renal brush border membrane were inhibited and those of carbohydrate metabolism were altered. There was an increase in DNA damage and DNA-protein cross-linking.”

Amino Acids • November 2013

Taurine ameliorates potassium bromate-induced kidney damage in rats

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Abstract

Potassium bromate (KBrO3) is widely used as a food additive and is a major water disinfection by-product. Several studies have shown that it causes nephrotoxicity in humans and experimental animals. We have investigated the potential role of the sulfonic amino acid taurine in protecting the kidney from KBrO3-induced damage in rats. Animals were randomly divided into four groups: control, KBrO3 alone, taurine alone and taurine + KBrO3. Administration of single oral dose of KBrO3 alone caused nephrotoxicity as evident by elevated serum creatinine and urea levels. Renal lipid peroxidation and protein carbonyls were increased while total sulfhydryl groups and reduced glutathione levels were decreased suggesting the induction of oxidative stress. The enzymes of renal brush border membrane were inhibited and those of carbohydrate metabolism were altered. There was an increase in DNA damage and DNA-protein cross-linking. Treatment with taurine, prior to administration of KBrO3, resulted in significant attenuation in all these parameters but the administration of taurine alone had no effect. Histological studies supported these biochemical results showing extensive renal damage in KBrO3-treated animals and greatly reduced tissue injury in the taurine + KBrO3 group. These results show that taurine is an effective chemoprotectant against bromate-induced renal damage and this amino acid could prove to be useful in attenuating the toxicity of this compound.

http://www.ncbi.nlm.nih.gov/pubmed/23913267

“Oral administration of 0.2% Potassium Bromate (KBrO3)
effectively induced epithelial tumors in the small intestines of Msh2-deficient mice.
We observed a 22.5-fold increase in tumor formation in the small intestines ...”

International Journal Of Biological Sciences • December 2013

Mismatch repair deficient mice show susceptibility to oxidative stress-induced intestinal carcinogenesis

Author information
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Abstract

We have previously established an experimental system for oxidative DNA damage-induced tumorigenesis in the small intestine of mice. To elucidate the roles of mismatch repair genes in the tumor suppression, we performed oxidative DNA damage-induced tumorigenesis experiments using Msh2-deficient mice. Oral administration of 0.2% Potassium Bromate, KBrO3, effectively induced epithelial tumors in the small intestines of Msh2-deficient mice. We observed a 22.5-fold increase in tumor formation in the small intestines of Msh2-deficient mice compared with the wild type mice. These results indicate that mismatch repair is involved in the suppression of oxidative stress-induced intestinal tumorigenesis in mice. A mutation analysis of the Ctnnb1 gene of the tumors revealed predominant occurrences of G:C to A:T transitions. The TUNEL analysis showed a decreased number of TUNEL-positive cells in the crypts of small intestines from the Msh2-deficient mice compared with the wild type mice after treatment of KBrO3. These results suggest that the mismatch repair system may simultaneously function in both avoiding mutagenesis and inducing cell death to suppress the tumorigenesis induced by oxidative stress in the small intestine of mice.

Full text with graphs, charts and 40 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879593/

> “We have shown that the renal carcinogens ochratoxin A (OTA) and potassium bromate (KBrO3) cause significant deciliation in a model of the proximal tubule.”

American Journal Of Physiology, Renal Physiology • April 2012

Carcinogens induce loss of the primary cilium in human renal proximal tubular epithelial cells independently of effects on the cell cycle

Author information

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Abstract

The primary cilium is an immotile sensory and signaling organelle found on the majority of mammalian cell types. Of the multitude of roles that the primary cilium performs, perhaps some of the most important include maintenance of differentiation, quiescence, and cellular polarity. Given that the progression of cancer requires disruption of all of these processes, we have investigated the effects of several carcinogens on the primary cilium of the RPTEC/TERT1 human proximal tubular epithelial cell line. Using both scanning electron microscopy and immunofluorescent labeling of the ciliary markers acetylated tubulin and Arl13b, we confirmed that RPTEC/TERT1 cells express primary cilium upon reaching confluence. Treatment with the carcinogens ochratoxin A (OTA) and potassium bromate (KBrO(3)) caused a significant reduction in the number of ciliated cells, while exposure to nifedipine, a noncarcinogenic renal toxin, had no effect on primary cilium expression. Flow cytometric analysis of the effects of all three compounds on the cell cycle revealed that only KBrO(3) resulted in an increase in the proportion of cells entering the cell cycle. Microarray analysis revealed dysregulation of multiple pathways affecting ciliogenesis and ciliary maintenance following OTA and KBrO(3) exposure, which were unaffected by nifedipine exposure. The primary cilium represents a unique physical checkpoint with relevance to carcinogenesis. We have shown that the renal carcinogens OTA and KBrO(3) cause significant deciliation in a model of the proximal tubule. With KBrO(3), this was followed by reentry into the cell cycle; however, deciliation was not found to be associated with reentry into the cell cycle following OTA exposure. Transcriptomic analysis identified dysregulation of Wnt signaling and ciliary trafficking in response to OTA and KBrO(3) exposure.

Full text with graphs, charts and 50 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3729533/

MOTILE CILIA

Larger eukaryotes, such as mammals, have what are called motile cilia. Motile cilia are usually present on a cell’s surface in large numbers and beat in coordinated waves. In humans, for example, motile cilia are found in the lining of the trachea (windpipe), where they sweep mucus and dirt out of the lungs. They’re also found in proximal tubules, explained below. In female mammals, the beating of cilia in the Fallopian tubes moves the ovum from the ovary to the uterus. The functioning of motile cilia is strongly dependent on the maintenance of optimal levels of fluid bathing the cilia. Epithelial sodium channels ENaC that are specifically expressed along the entire length of cilia apparently serve as sensors that regulate fluid level surrounding the cilia. Ciliates are microscopic organisms that possess motile cilia exclusively and use them for either locomotion or to simply move liquid over their surface. *See next page for further explanation.

PROXIMAL TUBULE

The human kidneys produce approximately 160–170 Liters of ultra-filtrate per day. The proximal tubule contributes to fluid, electrolyte, and nutrient homeostasis by reabsorbing approximately 60%–70% of the water and NaCl, a greater proportion of the NaHCO3, and nearly all of the nutrients in the ultra-filtrate. The proximal tubule is also the site of active solute secretion, hormone production, and many of the metabolic functions of the kidney. Damage to proximal tubule cilia reduces the ability of the proximal tubule to reabsorb nutrients and damages other functions.

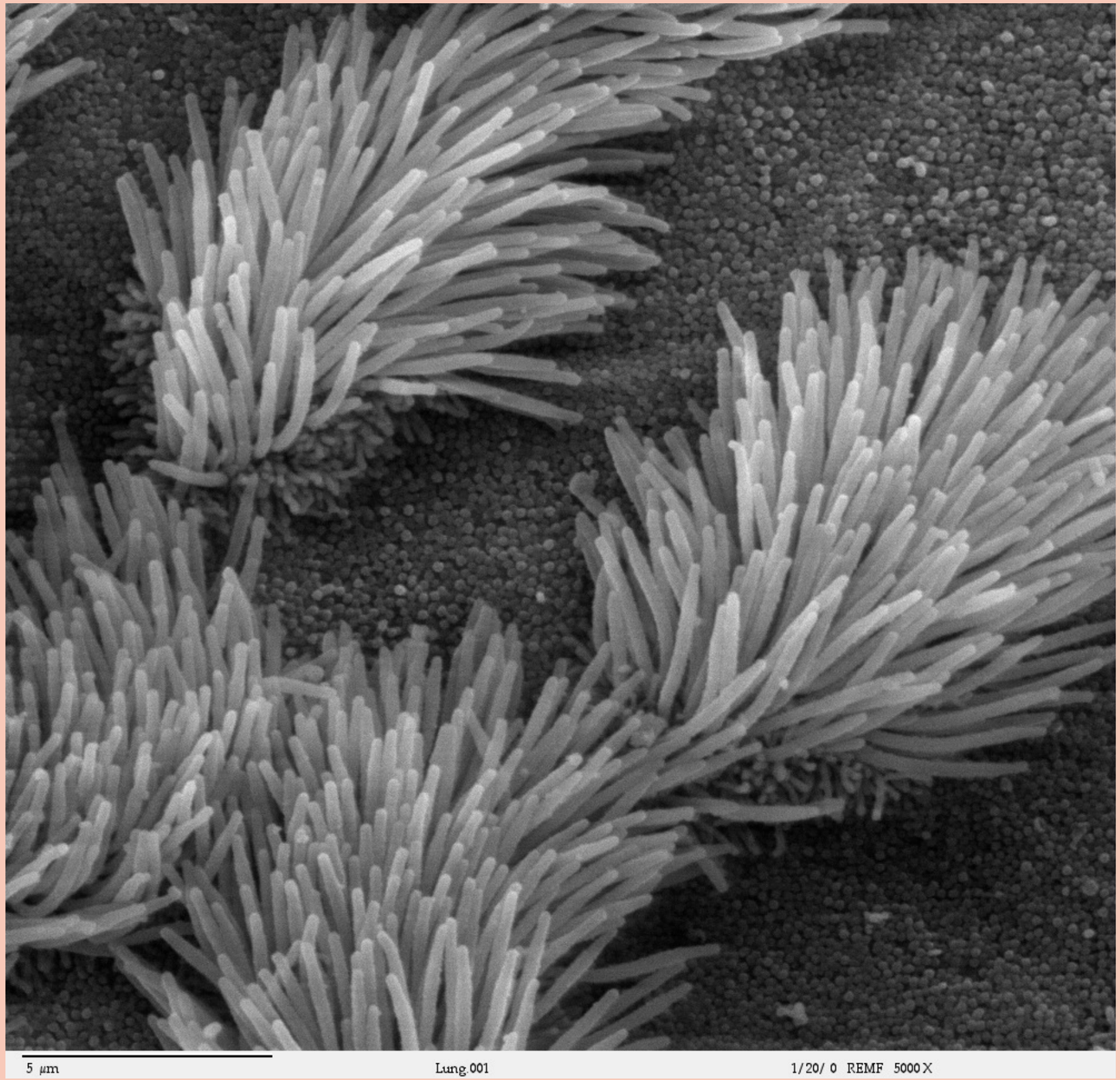
Cilium-related Disease

Ciliary defects can lead to a number of human diseases. Genetic mutations compromising the proper functioning of cilia, ciliopathies, can cause chronic disorders such as primary ciliary dyskinesia (PCD), nephronophthisis or Senior-Loken syndrome. In addition, a defect of the primary cilium in the renal tube cells can lead to polycystic kidney disease (PKD) as can potassium bromide. In another genetic disorder called Bardet-Biedl syndrome (BBS), the mutant gene products are the components in the basal body and cilia. Lack of functional cilia in female Fallopian tubes can cause ectopic pregnancy. A fertilized ovum may not reach the uterus if the cilia are unable to move it there. In such a case, the ovum will implant in the Fallopian tubes, causing a tubal pregnancy, the most common form of ectopic pregnancy.

Eepithelial sodium channels ENaC that are expressed along the length of cilia regulate fluid level surrounding the cilia. Mutations that decrease the activity of ENaC result in multisystem pseudohypoaldosteronism, that is associated with fertility problems. In cystic fibrosis that results from mutations in the chloride channel CFTR, ENaC activity is enhanced leading to a severe reduction of the fluid level that causes complications and infections in the respiratory airways.

Since the flagellum of human sperm is actually a modified cilium, ciliary dysfunction can also be responsible for male infertility, again implicating potassium bromate. Of interest, there is an association of primary ciliary dyskinesia with left-right anatomic abnormalities such as situs inversus (a combination of findings known as Kartagener's syndrome) and other heterotaxic defects. These left-right anatomic abnormalities can also result in congenital heart disease. In fact, it has been shown that proper cilial function is responsible for the normal left-right asymmetry in mammals. Obviously you can see how critically important robust and healthy cilia are to human health.

Pictured at right, healthy lung cilia at 5000X magnification.



“These results show for the first time that Potassium bromate (KBrO3) induces oxidative stress in blood and impairs the anti-oxidant defense system.”

Chemosphere • May 2012

Oral administration of potassium bromate, a major water disinfection by-product, induces oxidative stress and impairs the antioxidant power of rat blood

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Abstract

Potassium bromate (KBrO(3)) is a widely used food additive, a water disinfection by-product and a known nephrotoxic agent. The effect of KBrO(3) on rat blood, especially on the anti-oxidant defense system, was studied in this work. Animals were given a single oral dose of KBrO(3) (100 mg/kg body weight) and sacrificed 12, 24, 48, 96 and 168 h after this treatment. Blood was collected from the animals and separated into plasma and erythrocytes. KBrO(3) administration resulted in increased lipid peroxidation, protein oxidation, hydrogen peroxide levels and decreased the reduced glutathione content indicating the induction of oxidative stress in blood. Methemoglobin levels and methemoglobin reductase activity were significantly increased while the total anti-oxidant power was greatly reduced upon KBrO(3) treatment. Nitric oxide levels were enhanced while vitamin C concentration decreased in KBrO(3) treated animals. The activities of major anti-oxidant enzymes were also altered upon KBrO(3) treatment. The maximum changes in all these parameters were 48 h after the administration of KBrO(3) and then recovery took place. These results show for the first time that KBrO(3) induces oxidative stress in blood and impairs the anti-oxidant defense system. Thus impairment in the anti-oxidant power and alterations in the activities of major anti-oxidant enzymes may play an important role in mediating the toxic effects of KBrO(3) in the rat blood. The study of such biochemical events in blood will help elucidate the molecular mechanism of action of KBrO(3) and also for devising methods to overcome its toxic effects.

http://www.ncbi.nlm.nih.gov/pubmed/22277885

BMC Complementary Alternative Medicine • November 2012

Protective effects of rutin against potassium bromate induced nephrotoxicity in rats

By Khan RA, Khan MR and Sahreen S.

Abstract

BACKGROUND

Rutin, a polyphenolic flavonoid, was investigated for its protective effects against the KBrO(3) induced renal injuries in rat.

METHODS

Group I was control (untreated), group II was given saline 0.5 ml/kg bw (0.9% NaCl), group III was administered KBrO(3) (20 mg/kg bw) intragastric twice a week for four weeks. Rutin was administered to group VI (50 mg/kg bw) and Group V (70 mg/kg bw) along with KBrO(3) (20 mg/kg bw) while group VI was given rutin (70 mg/kg bw) alone twice a week for four weeks. Protective effects of rutin on KBrO(3)-induced nephrotoxicity in rats were determined for biochemical parameter of urine, and serum, various antioxidant enzymes, DNA and histopathological damages in kidneys.

RESULTS

The level of urinary red blood cells, leucocytes count, specific gravity, urea, creatinine and urobilinogen was increased (P<0.01) whereas creatinine clearance was reduced. Serum level of protein, albumin, globulin, nitrite, creatinine and blood urea nitrogen (BUN) was significantly increased (P<0.01) by KBrO(3). Marked histopathological lesions, elevated DNA fragmentation and AgNORs count in renal tissues was determined. Activity of antioxidant enzymes; catalase, superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, glutathione reductase, and reduced glutathione contents were decreased (P<0.01) while thiobarbituric acid reactive substances were increased (P<0.01) with KBrO(3) treatment in kidneys. DNA ladder assay was intimately related with the DNA fragmentation assay. Telomerase activity was found positive in the KBrO(3) treated kidneys. Treatment with rutin effectively ameliorated the alterations in the studied parameters of rat. Rutin administration alone to rats did not exhibit any significant change in any of the parameters studied.

CONCLUSION

These results suggest that rutin works as an antioxidant in vivo by scavenging reactive oxygen species and this serves to prevent oxidative renal damage in rat treated with KBrO(3).

Full text with graphs, charts and 65 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3552874/

“The level of urinary red blood cells, leucocytes count, specific gravity, urea, creatinine and urobilinogen was increased (P<0.01) whereas creatinine clearance was reduced. Serum level of protein, albumin, globulin, nitrite, creatinine and blood urea nitrogen (BUN) was significantly increased (P<0.01) by KBrO(3). Marked histopathological lesions, elevated DNA fragmentation and AgNORs count in renal tissues was determined. Activity of antioxidant enzymes; catalase, superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, glutathione reductase, and reduced glutathione contents were decreased (P<0.01) while thiobarbituric acid reactive substances were increased (P<0.01) with KBrO(3) treatment in kidneys. DNA ladder assay was intimately related with the DNA fragmentation assay. Telomerase activity was found positive in the KBrO(3) treated kidneys.”

“Potassium bromate (KBrO3) is an oxidising agent that has been widely used in the food and cosmetic industries. It has shown to be both a nephrotoxin and a renal carcinogen in in-vivo and in-vitro models.”

Archives In Toxicology • November 2012

Oxidative stress induced by potassium bromate exposure results in altered tight junction protein expression in renal proximal tubule cells

Author information

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Abstract

Potassium bromate (KBrO(3)) is an oxidising agent that has been widely used in the food and cosmetic industries. It has shown to be both a nephrotoxin and a renal carcinogen in in vivo and in vitro models. Here, we investigated the effects of KBrO(3) in the human and rat proximal tubular cell lines RPTEC/TERT1 and NRK-52E. A genome-wide transcriptomic screen was carried out from cells exposed to a sub-lethal concentration of KBrO(3) for 6, 24 and 72 h. Pathway analysis identified “glutathione metabolism”, “Nrf2-mediated oxidative stress” and “tight junction (TJ) signalling” as the most enriched pathways. TJ signalling was less impacted in the rat model, and further studies revealed low transepithelial electrical resistance (TEER) and an absence of several TJ proteins in NRK-52E cells. In RPTEC/TERT1 cells, KBrO(3) exposure caused a decrease in TEER and resulted in altered expression of several TJ proteins. N-Acetylcysteine co-incubation prevented these effects. These results demonstrate that oxidative stress has, in conjunction with the activation of the cytoprotective Nrf2 pathway, a dramatic effect on the expression of tight junction proteins. The further understanding of the cross-talk between these two pathways could have major implications for epithelial repair, carcinogenesis and metastasis.

http://www.ncbi.nlm.nih.gov/pubmed/22760423

“Lipid peroxidation, protein oxidation and hydrogen peroxide levels increased while total sulfhydryl groups and reduced glutathione decreased in KBrO(3)-treated rats indicating induction of oxidative stress in the intestinal mucosa. The activities of anti-oxidant and carbohydrate metabolic enzymes were also altered upon KBrO(3) treatment. These results show that a single oral dose of KBrO(3) causes reversible oxidative damage to the intestine.”

Biochimie • December 2012

Alterations in brush border membrane enzymes, carbohydrate metabolism and oxidative damage to rat intestine by potassium bromate

Author information

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Abstract

The acute toxicity of potassium bromate (KBrO(3)) on rat small intestine was studied in this work. Animals were given a single oral dose of KBrO(3) (100 mg/kg body weight) and sacrificed 12, 24, 48, 96 and 168 h after the treatment; control animals were not given KBrO(3). The administration of KBrO(3) resulted in a reversible decline in the specific activities of several BBM enzymes. Lipid peroxidation, protein oxidation and hydrogen peroxide levels increased while total sulfhydryl groups and reduced glutathione decreased in KBrO(3)-treated rats indicating induction of oxidative stress in the intestinal mucosa. The activities of anti-oxidant and carbohydrate metabolic enzymes were also altered upon KBrO(3) treatment. The maximum changes in all the parameters were 48 h after administration of KBrO(3) after which recovery took place, in many cases almost to control values after 168 h. Histopathological studies supported the biochemical findings showing extensive damage to the intestine at 48 h and recovery at 168 h. These results show that a single oral dose of KBrO(3) causes reversible oxidative damage to the intestine.

http://www.ncbi.nlm.nih.gov/pubmed/22974983

“Importantly, compounds with established links to chronic renal toxicity produced more diverse and severe perturbations to the cellular metabolome than non-toxic compounds in this model..”

Molecular Biosystems • January 2011

Metabolic response to low-level toxicant exposure in a novel renal tubule epithelial cell system

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Abstract

Toxicity testing is vital to protect human health from exposure to toxic chemicals in the environment. Furthermore, combining novel cellular models with molecular profiling technologies, such as metabolomics can add new insight into the molecular basis of toxicity and provide a rich source of biomarkers that are urgently required in a 21st Century approach to toxicology. We have used an NMR-based metabolic profiling approach to characterise for the first time the metabolome of the RPTEC/TERT1 cell line, an immortalised non-tumour human renal epithelial cell line that recapitulates phenotypic characteristics that are absent in other in vitro renal cell models. RPTEC/TERT1 cells were cultured with either the dosing vehicle (DMSO) or with exposure to one of six compounds (nifedipine, potassium bromate, monuron, D-mannitol, ochratoxin A and sodium diclofenac), several of which are known to cause renal effects. Aqueous intracellular and culture media metabolites were profiled by (1)H NMR spectroscopy at 6, 24 and 72 hours of exposure to a low effect dose (IC(10)). We defined the metabolome of the RPTEC/TERT1 cell line and used a principal component analysis approach to derive a panel of key metabolites, which were altered by chemical exposure. By considering only major changes (±1.5 fold change from control) across this metabolite panel we were able to show specific alterations to cellular processes associated with chemical treatment. Our findings suggest that metabolic profiling of RPTEC/TERT1 cells can report on the effect of chemical exposure on multiple cellular pathways at low-level exposure, producing different response profiles for the different compounds tested with a greater number of major metabolic effects observed in the toxin treated cells. Importantly, compounds with established links to chronic renal toxicity produced more diverse and severe perturbations to the cellular metabolome than non-toxic compounds in this model. As these changes can be rationalised with the different pharmacological and toxicity profiles of the chemicals it is suggested that metabolic profiling in the RPTEC/TERT1 model would be useful in investigating the mechanism of action of toxins at a low dose.

http://www.ncbi.nlm.nih.gov/pubmed/21103459

“These results suggest that Potassium Bromate exerts oxidative stress and genotoxic effects in HepG2 cells, possibly through the mechanisms of lysosomal damage, an earlier event preceding the oxidative DNA damage..”

Chemical & Biological Interactions • February 2011

Possible involvement of oxidative stress in potassium bromate-induced genotoxicity in human HepG2 cells

Author information

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Abstract

Potassium bromate (KBrO(3), PB) is a by-product of ozone used as disinfectant in drinking water. And PB is also a widely used food additive. However, there is little known about its adverse effects, in particular those related to its genotoxicity in humans. The aim of this study was to investigate the genotoxic effects of PB and the underlying mechanisms, using human hepatoma cell line, HepG2. Exposure of the cells to PB caused a significant increase of DNA migration in single cell gel electrophoresis (SCGE) assay and micronuclei (MN) frequencies in micronucleus test (MNT) at all tested concentrations (1.56-12.5 mM and 0.12-1 mM), which suggested that PB-mediated DNA strand breaks and chromosome damage. To indicate the role of antioxidant in those effects, DNA migration was monitored by pre-treatment with hydroxytyrosol (HT) as an antioxidant in SCGE assay. It was found that DNA migration with pre-treatment of HT was dramatically decreased. To elucidate the genotoxicity mechanisms, the study monitored the levels of reactive oxygen species (ROS), glutathione (GSH) and 8-hydroxydeoxyguanosine (8-OHdG). PB was shown to induce ROS production (12.5 mM), GSH depletion (1.56-12.5 mM) and 8-OHdG formation (6.25-12.5 mM) in HepG2 cells. Moreover, lysosomal membrane stability and mitochondrial membrane potential were further studied for the mechanisms of PB-induced genotoxicity. A significant increase was found in the range of 6.25-12.5 mM in lysosomal membrane stability assay. However, under these PB concentrations, we were not able to detect the changes of mitochondrial membrane potential. These results suggest that PB exerts oxidative stress and genotoxic effects in HepG2 cells, possibly through the mechanisms of lysosomal damage, an earlier event preceding the oxidative DNA damage.

http://www.ncbi.nlm.nih.gov/pubmed/21182833

Hep G2 Cells

Hep G2 is a human liver cancer cell line. Hep G2 is a perpetual cell line which was derived from the liver tissue of a 15-year-old Caucasian American male with a well-differentiated hepatocellular carcinoma. They have been grown successfully in large-scale cultivation systems. HepG2 will respond to stimulation with human growth hormone. Because of their high degree of morphological and functional differentiation in vitro, HepG2 cells are a suitable model to study human liver diseases and their derivatives are also used as a model system for studies of liver metabolism and toxicity of xenobiotics, the detection of environmental and dietary cytotoxic and genotoxic agents, understanding hepatocarcinogenesis, and for drug targeting studies. HepG2 cells are also employed in trials with bioartificial liver devices.

Toxicology • January 2010

Anomalous genotoxic responses induced in mouse lymphoma L5178Y cells by potassium bromate

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> "Results confirmed that it is a potent genotoxin in mouse lymphoma L5178Y cells inducing micronuclei and mutation at the tk and hprt loci at relatively non-cytotoxic concentrations."

Abstract

Potassium bromate (KBrO3) is a well-established rodent kidney carcinogen and its oxidising activity is considered to be a significant factor in its mechanism of action. Although it has also been shown to be clearly genotoxic in a range of in vivo and in vitro test systems, surprisingly, it is not readily detected in several cell lines using the standard alkaline Comet assay. However, previous results from this laboratory demonstrated huge increases in tail intensity by modifying the method to include incubation with either human 8-oxodeoxyguanosine DNA glycosylase-1 (hOGG1) or bacterial formamidopyrimidine DNA glycosylase (FPG) indicating that, as expected, significant amounts of 8-oxodeoxyguanosine (8-OHdG) were induced. The purpose of this work, therefore, was to investigate why KBrO3, in contrast to other oxidising agents, gives a relatively poor response in the standard Comet assay. Results confirmed that it is a potent genotoxin in mouse lymphoma L5178Y cells inducing micronuclei and mutation at the tk and hprt loci at relatively non-cytotoxic concentrations. Subsequent time-course studies demonstrated that substantial amounts of 8-OHdG appear to remain in cells 24h after treatment with KBrO3 but result in no increase in frank stand breaks (FSB) even though phosphorylated histone H2AX (gamma-H2AX) antibody labelling confirmed the presence of double-strand breaks. Using bromodeoxyuracil (BrdU) incorporation together with measured increases in cell numbers, L5178Y cells also appeared to go through the cell cycle with unrepaired hOGG1-recognisable damage. Since unrepaired 8-OHdG can give rise to point mutations through G:C-->T:A transversions, it was also surprising that mutation could not be detected at the Na+/K+ATPase locus as determined by ouabain resistance. Some increases in strand breakage could be seen in the Comet assay by increasing the unwinding time, but only at highly toxic concentrations and to a much smaller extent than would be expected from the magnitude of the other genotoxic responses. It was considered unlikely that these anomalous observations were due to the inability of L5178Y cells to recognise 8-OHdG because these cells were shown to express mOGG1 and have functional cleavage activity at the adducted site. It appears that the responses of L5178Y cells to KBrO3 are complex and differ from those induced by other oxidising agents.

http://www.ncbi.nlm.nih.gov/pubmed/19853637

“The similar mode of action in both Normal Rat Kidney cells suggests that the mechanisms of Potassium Bromate-induced renal cell death are model-independent ...”

Toxicology • February 2010

Cellular and molecular mechanisms of bromate-induced cytotoxicity in human and rat kidney cells

Author information

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Abstract

The mechanisms of bromate (BrO(3)(-))-induced toxicity in Normal Rat Kidney (NRK) and human embryonic kidney 293 (HEK293) cells were investigated. BrO(3)(-) (added as KBrO(3)) induced concentration-dependent decreases in 3-(4, dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (MTT) staining after 48 h. BrO(3)(-)-induced necrosis based on tandem increases in annexin V and PI staining. Cell cycle analysis demonstrated that BrO(3)(-) also induced G2/M arrest and nuclear fragmentation, prior to alterations in MTT staining or annexin V and PI staining. Immunoblot analysis demonstrated that the G2/M arrest correlated to induction of phosphorylated (p)-p53, p21, cyclin B1 and p-cdc2. Further, BrO(3)(-) induced time-dependent increases in the activity of the mitogen activated protein kinases p38 and ERK1/2. Treatment of cells with the p38 inhibitor SB202190, but not the ERK1/2 inhibitor PD98059, partially reversed BrO(3)(-)-induced G2/M arrest and decreased BrO(3)(-)-induced p-p53, p21 and cyclin B1 expression. In addition, BrO(3)(-) treatment induced reactive oxygen species (ROS) based on increases in CM-H(2)DCFDA fluorescence. The antioxidant ascorbic acid inhibited BrO(3)(-)-induced p38 activation, G2/M arrest, p-p53, p21 and cyclin B1 expression; however, ascorbic acid had no effect on BrO(3)(-)-induced formation of 8-OHdG, a marker of DNA oxidative damage, whose increases preceded cell death by 24h. These data suggest that ROS mediated MAPK activation is involved in the molecular mechanisms of BrO(3)(-)-induced cell cycle arrest, which occurs independently of 8-OH-dG production. The similar mode of action in both NRK and HEK293 cells suggests that the mechanisms of BrO(3)(-)-induced renal cell death are model-independent.

http://www.ncbi.nlm.nih.gov/pubmed/20067818

“Their [referring to potassium bromate and hydrogen peroxide] downstream target genes and signalling pathways were subsequently activated leading mainly to the induction of antioxidant defenses, inflammation, cell cycle arrest, DNA repair and cell death..”

Mutation Research • July 2010

Study of gene expression profiles in TK6 human cells exposed to DNA-oxidizing agents

Author information
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Abstract

During the last decade, there has been clear progress in using threshold in risk assessment but its acceptance by scientists is still under debate. Contrary to indirect DNA-damaging agents, DNA-reactive agents have been assumed to have a non-threshold mode of action, as they directly induce DNA lesions that potentially can be converted into mutations. However, in recent years there is a growing number of data establishing threshold doses even for these DNA-reactive compounds. Indeed, there are several defence and repair mechanisms that provide protection and that may be responsible for genotoxic thresholds. In this context, we recently showed that DNA-oxidizing agents exhibit a thresholded dose-response in vitro with respect to chromosomal alterations. We have hypothesized the involvement of different cellular responses whose nature and efficiency depend on the stress level. The aim of this study was to develop a more complete understanding of these underlying mechanisms. We investigated global gene expression profiles of human lymphoblastoid TK6 cells after exposure to potassium bromate and hydrogen peroxide (via glucose oxidase). Cells were treated for 1h and mRNAs were isolated either immediately at the end of the treatment or after a 23-h recovery period. Our results showed that cells have developed elaborate cellular responses to oxidative stress in order to maintain genomic integrity. Many of altered genes were redox-sensitive transcription factors such as p53, NF-kappaB, AP-1 and Nrf2. Their downstream target genes and signalling pathways were subsequently activated leading mainly to the induction of antioxidant defenses, inflammation, cell cycle arrest, DNA repair and cell death. Overall, our study allowed the identification of key events involved in the thresholded response observed after DNA-oxidizing agents exposure and shows the usefulness of the combination of standard in vitro genotoxicity assays with gene expression profiling technology to determine modes of action, particularly for critical risk assessment.

http://www.ncbi.nlm.nih.gov/pubmed/20466008

“Potassium bromate induces oxidative stress and may contribute to neoplasia in endocrine glands. It has been demonstrated that Potassium bromate triggers thyroid follicular cell tumors in rats. It has been revealed in our in vivo and in vitro studies that Potassium bromate significantly increases lipid peroxidation in rat and porcine thyroid. Potassium bromate also induces mesotheliomas ... Potassium bromate is a pro-oxidant which may induce neoplasia in endocrine glands and cause hormonal disturbances ....”

Endokrynologia Polska • January 2009

Relationship between toxic effects of potassium bromate and endocrine glands

Author information
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Abstract

Potassium bromate (KBrO(3)) is a compound belonging to Group 2B of carcinogens (a possible human carcinogen). This agent was used as a food additive in flour treatment, as a component of cold-wave hair lotions, and is still used in barley processing. Additionally, KBrO(3) is formed as an oxyhalide by-product during water ozonation. KBrO(3) induces oxidative stress and may contribute to neoplasia in endocrine glands. It has been demonstrated that KBrO(3) triggers thyroid follicular cell tumors in rats. It has been revealed in our in vivo and in vitro studies that KBrO(3) significantly increases lipid peroxidation in rat and porcine thyroid. KBrO(3) also induces mesotheliomas which may secrete hormones or similar substances, such as parathyroid hormone related protein, phosphatonins or melanocyte stimulating hormone. In our experimental studies we demonstrated that antioxidants, such as pineal hormone - melatonin, indole-3-propionic acid (IPA) (a compound chemically and physically similar to melatonin) and antythyroid drug - propylthiouracil (PTU), produce distinct protective effects against lipid peroxidation due to KBrO(3) in the thyroid in vivo. KBrO(3) is a prooxidant which may induce neoplasia in endocrine glands and cause hormonal disturbances, however its damaging effects may be neutralized by hormones, mainly melatonin.

http://www.ncbi.nlm.nih.gov/pubmed/19224504

“Potassium bromate is injurious to health if consumed continuously and in high quantity. It has been shown to reduce platelet count in rats, and thus may cause thrombocytopenia in humans. It is therefore imperative to take adequate measures to eliminate the use of potassium bromate in the preparation of food products..”

Niger Journal Of Physiological Sciences • June 2009

The effect of potassium bromate on some haematological parameters of Wistar rats

Author information

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Abstract

Potassium bromate used widely in foods has been associated with various complications in humans. However there is paucity of literature on adverse effects on haematological parameters. Thus we decided to carry out an experimental study to determine the effects of potassium bromate on some blood indices using Wistar rats. Twenty (20) male Wistar rats aged 2-3 months obtained from the department of Veterinary Medicine, University of Nigeria Nsukka were acclimatized for two weeks. They were divided into five groups and fed with graded doses of potassium bromate solution for six weeks. One of the groups served as the control. Pre and post administration blood samples were collected and analyzed the same day using standard methods. The results revealed significant [$P<0.05$] decrease in the platelet count when compared with the controls. There were no statistically significant differences in the mean cell haemoglobin concentration, haematocrit, and total leukocyte counts between the test and control rats. Potassium bromate is injurious to health if consumed continuously and in high quantity. It has been shown to reduce platelet count in rats, and thus may cause thrombocytopenia in humans. It is therefore imperative to take adequate measures to eliminate the use of potassium bromate in the preparation of food products.

http://www.ncbi.nlm.nih.gov/pubmed/19826465

Food Chemistry Toxicology • June 2009

Early alterations in protein and gene expression in rat kidney following bromate exposure

Author information

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Abstract

"Bromate, a common disinfectant byproduct of drinking water ozonation, has been linked to human and animal renal toxicity, including renal cell carcinomas in multiple animal species. Here, we evaluate changes in protein and gene expression through two-dimensional difference gel electrophoresis (2D-DIGE) and Affymetrix arrays to identify potential modes of action involved in potassium bromate carcinogenicity. Male rats were exposed to potassium bromate in drinking water at concentrations of 0, 1, 20 and 400 ppm for two weeks. Differential expression of glycolytic proteins including enolase 1 (Eno1), triosephosphate isomerase 1 (Tpi1) and glyceraldehyde-3-phosphate dehydrogenase (Gapdh) suggests that bromate toxicity is associated with changes in energy consumption and utilization in renal cells involving up-regulation of glycolytic processes that may be the result of altered mitochondrial function. Several alterations in glycolysis and mitochondrial gene transcripts were also observed to be consistent with this mode of action. These studies provide insight into early events in renal cell physiology altered by bromate exposure..."

http://www.ncbi.nlm.nih.gov/pubmed/19425233

“The aim of this study was to investigate the genotoxic effects of potassium bromate ... These in vitro results provide important evidence about genotoxicity of potassium bromate on a human cell culture system.”

Mutation Research • January 2007

Genotoxic effects of potassium bromate on human peripheral lymphocytes in vitro

Author information

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Abstract

The aim of this study was to investigate the genotoxic effects of potassium bromate, which is used as a bleaching agent in flour, on human peripheral blood lymphocytes in vitro by sister chromatid exchange (SCE), chromosomal aberrations (CA) and micronucleus (MN) tests, and also to determine whether it has any genotoxic potential for humans. Cells were treated with 400, 450, 500, 550 microg/ml concentrations of potassium bromate for 24 and 48 h. The SCE frequencies showed an increase after both treatment periods, however, the differences between the treated cells and the control groups were found to be statistically significant only for the 48-h treatment. In addition, potassium bromate statistically significantly induced CA after the 24-h and 48-h treatment periods. Strikingly, potassium bromate induced CA as much as the positive control, mitomycin-C (MMC). Furthermore, potassium bromate decreased both the cell proliferation index (PI) and the mitotic index (MI). Although micronucleus formation was induced by potassium bromate during the 24-h treatment period in a dose-dependent manner, only the doses 500 and 550 microg/ml yielded statistically significant results. In contrast, MN formation was significantly induced at all doses during the 48-h treatment period. These in vitro results provide important evidence about genotoxicity of potassium bromate on a human cell culture system.

http://www.ncbi.nlm.nih.gov/pubmed/17118698

“After a 4-hour treatment, the alkaline and neutral comet assay demonstrated that Potassium bromate directly yielded DNA damages including DNA double strand breaks. Potassium bromate also induced micronucleus and thymidine kinase mutations concentration-dependently. At the highest concentration (5mM), Potassium bromate induced micronucleus and thymidine kinase mutation frequencies that were over 30-times the background level. Molecular analysis revealed that 90% of the induced mutations were large deletions that involved loss of heterozygosity at the thymidine kinase locus..”

Mutation Research • June 2007

Potassium bromate treatment predominantly causes large deletions, but not GC>TA transversion in human cells

Author information
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Abstract

Potassium bromate (KBrO(3)) is strongly carcinogenic in rodents and mutagenic in bacteria and mammalian cells in vitro. The proposed genotoxic mechanism for KBrO(3) is oxidative DNA damage. KBrO(3) can generate high yields of 8-hydroxydeoxyguanosine (8OHdG) DNA adducts, which cause GC>TA transversions in cell-free systems. In this study, we investigated the in vitro genotoxicity of KBrO(3) in human lymphoblastoid TK6 cells using the comet (COM) assay, the micronucleus (MN) test, and the thymidine kinase (TK) gene mutation assay. After a 4h treatment, the alkaline and neutral COM assay demonstrated that KBrO(3) directly yielded DNA damages including DNA double strand breaks (DSBs). KBrO(3) also induced MN and TK mutations concentration-dependently. At the highest concentration (5mM), KBrO(3) induced MN and TK mutation frequencies that were over 30 times the background level. Molecular analysis revealed that 90% of the induced mutations were large deletions that involved loss of heterozygosity (LOH) at the TK locus. Ionizing-irradiation exhibited similar mutational spectrum in our system. These results indicate that the major genotoxicity of KBrO(3) may be due to DSBs that lead to large deletions rather than to 8OHdG adducts that lead to GC>TA transversions, as is commonly believed. To better understand the genotoxic mechanism of KBrO(3), we analyzed gene expression profiles of TK6 cells using Affymetrix Genechip. Some genes involved in stress, apoptosis, and DNA repair were up-regulated by the treatment of KBrO(3). However, we could not observe the similarity of gene expression profile in the treatment of KBrO(3) to ionizing-irradiation as well as oxidative damage inducers.

http://www.ncbi.nlm.nih.gov/pubmed/17428505

Archives In Toxicology • October 2007

Renal deterioration caused by carcinogens as a consequence of free radical mediated tissue damage: a review of the protective action of melatonin

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Abstract

“This brief review summarizes some of the publications that document the preventive role of melatonin in kidney damage caused by carcinogens such as 2-nitropropane, arsenic, carbon tetrachloride, nitrilotriacetic acid and potassium bromate. Numerous chemicals generate excessive free radicals that eventually induce renal worsening. Melatonin partially or totally prevents free radical mediated tissue damages induced by many carcinogens. Protective actions of melatonin against the harmful effects of carcinogens are believed to stem from its direct free radical scavenging and indirect antioxidant activities. Dietary or pharmacologically given melatonin may attenuate the oxidative stress, thereby mitigating the subsequent renal damage.”

http://www.ncbi.nlm.nih.gov/pubmed/17823789

Toxicology • April 2006

Etiology of bromate-induced cancer and possible modes of action-studies in Japan

Author information
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Abstract

Renal cell tumors were significantly increased in male and female rats given potassium bromate at 250 and 500 mg/L in drinking water. In at least one other study renal cell tumors were produced in male rats at 125 mg/L. Among male mice given 750 mg/L of potassium bromate, there were no significant differences in renal cell tumors between treated and control groups after 88 weeks on test. In oxidative DNA damage tests 8-oxodeoxyguanosine (8-oxodG also referred to as 8-OH-dG) was induced in DNA in the male rat kidney in 1 week, and in females after 3 weeks at 500 mg/L, and also in both male and female rats at 250 mg/L, but not at 125 mg/L. DNA adducts are considered to be an initial step in the carcinogenesis process, however, the administered doses are not always sufficient to cause mutations, possibly due to DNA repair. In the two-step rat renal carcinogenesis model using N-ethyl-N-hydroxyethylnitrosamine (EHEN) as initiator, promotion activity by potassium bromate was measured using the BrdU labeling index. The promoting activity of bromate in male rats was much greater and extended to doses as low as 60 mg/L in male rats, whereas in females the response was limited to 250 and 500 mg/L. Therefore, it was concluded that the mechanisms contributing to cancer in the male rat were more complex than in the female rat. The accumulation of alpha2mu-globulin in the kidneys of male rats exposed to potassium bromate probably accounts for the greater labeling index in the male rat relative to the female rat. Accumulation of alpha(2mu)-globulin as a result of treatment with chemicals is unique to the male rat and does contribute to carcinogenic responses. Neither humans nor female rats display this response. Nevertheless, bromate must be considered carcinogenic because of the response of the female rats. The better correlation between 8-oxodG formation and tumor response indicates that dose-response information from the female rat would be much more relevant to human risk assessment. The fact that an elevation of BrdU-LI in the kidney of the female rat is consistent with the possibility that cell proliferation observed in female rats resulted from oxidative stress and/or cytotoxic responses in the kidney. Therefore, oxidative stress is most likely the mechanism of interest for cancer risk in humans.

http://www.ncbi.nlm.nih.gov/pubmed/16473452

“Renal cell tumors were significantly increased in male and female rats given potassium bromate at 250 and 500 mg/L in drinking water. The promoting activity of bromate in male rats was much greater and extended to doses as low as 60 mg/L in male rats, whereas in females the response was limited to 250 and 500 mg/L. Therefore, it was concluded that the mechanisms contributing to cancer in the male rat were more complex than in the female rat ... oxidative stress is most likely the mechanism of interest for cancer risk in humans..”

Potassium bromate is classified as a category 2B carcinogen (possibly carcinogenic to humans) by the International Agency for Research on Cancer (IARC), notoriously and sickeningly beholden to multinational corporate profits and the needs of the chemical makers. Potassium bromate has been banned from use in food products in the European Union, Argentina, Brazil, Canada, Nigeria, South Korea, Peru and many other countries. It was banned in Sri Lanka in 2001 and China in 2005. In the United States of America it hasn’t been banned. The FDA sanctioned the use of bromate before the Delaney clause of the Food, Drug, and Cosmetic Act—which bans potentially carcinogenic substances— and which went into effect in 1958. But since 1991 the FDA has urged bakers to voluntarily stop using it. In California a warning label is required when bromated flour is used. Japanese baked goods manufacturers stopped using potassium bromate voluntarily in 1980; however, Yamazaki Baking resumed its use in 2005, claiming they had new production methods to reduce the amount of the chemical which remained in the final product.

“Therefore, mechanism of bromate-induced oxidative DNA damage is different from general types of oxidative stress such as hydroxyl radical (*OH)..”

Toxicology • April 2006

Mechanism of DNA damage induced by bromate differs from general types of oxidative stress

Author information
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Abstract

A representative reactive oxygen species (ROS), hydroxyl radical (*OH), is a highly reactive species and induces DNA backbone breakage. *OH also oxidizes every DNA base. The interaction of *OH with guanine leads to the generation of not only piperidine-resistant 8-oxo-7,8-dihydro-2’-deoxyguanosine (8-oxodG) but also various piperidine-labile products. On the other hand, potassium bromate (KBrO3) induces specific formation of 8-oxodG in the presence of SH compounds, such as glutathione (GSH) and cysteine (Cys). GSH/Cys reduces KBrO3 (BrO3-) to BrO2, which abstracts one electron from guanine. The one-electron oxidation of guanine may yield cation radicals followed by the reaction with a water molecule, leading to 8-oxodG formation. Therefore, mechanism of bromate-induced oxidative DNA damage is different from general types of oxidative stress such as hydroxyl radical *OH.

http://www.ncbi.nlm.nih.gov/pubmed/16457930

“For decades, it has been known that ingested potassium bromate and sodium bromate can induce hearing loss. The effects of long-term low-dose bromate exposure on hearing have not been studied. These effects, if they occur, may not be readily detected in many clinical populations, because idiopathic hearing loss occurs commonly in the population as a whole. Further it is unknown whether or not chronic bromate ingestion may exacerbate noise-induced hearing loss.”

Toxicology • April 2006

Bromate-induced ototoxicity

Author information

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Abstract

For decades, it has been known that ingested potassium bromate and sodium bromate can induce hearing loss. Hearing loss onset, following high-dose ingestion, is generally rapid occurring within 4-16 h and of a severe to profound degree. Unlike the sensorineural hearing loss which is generally irreversible, bromate-induced tinnitus, which is less well-studied, may reportedly be permanent or temporary. It is not clear whether actual bromate-induced vestibulotoxicity occurs in clinical populations. The primary sites of lesion for bromate-induced ototoxicity appear to be in the cochlea. However, possible effects on the VIIIth nerve and central auditory system have not been fully investigated. Based on animal studies, in the cochlea, bromate damages the stria vascularis, Reissner’s membrane, inner and outer hair cells, Claudius cells and inner sulcus cells. Physiologically, bromate reduces the endocochlear potential, cochlear microphonics, and electrophysiologic auditory thresholds. Possible mechanisms are discussed. The effects of long-term low-dose bromate exposure on hearing have not been studied. These effects, if they occur, may not be readily detected in many clinical populations, because idiopathic hearing loss occurs commonly in the population as a whole. Further it is unknown whether or not chronic bromate ingestion may exacerbate noise-induced hearing loss. Further study to determine the maximum safe exposure level for long-term administration and to develop possible antidotes is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/16460859

“... oxidative DNA damage and the induction of mutations and micronuclei is easily detectable at non-cytotoxic concentrations of bromate ...”

Toxicology • April 2006

DNA damage by bromate: mechanism and consequences

Author information

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Abstract

Exposure of mammalian cells to bromate (BrO3-) generates oxidative DNA modifications, in particular 7,8-dihydro-8-oxo-guanine (8-oxoG). The damaging mechanism is quite unique, since glutathione, which is protective against most oxidants and alkylating agents, mediates a metabolic activation, while bromate itself does not react directly with DNA. Neither enzymes nor transition metals are required as catalysts in the activation. The ultimate DNA damaging species has not yet been established, but experiments under cell-free conditions suggest that neither molecular bromine nor reactive oxygen species such as superoxide, hydrogen peroxide or singlet oxygen are involved. Rather bromine radicals (Br*) or oxides (BrO*, BrO2*) might be responsible. Compared to hypochlorite (ClO-), bromate is much less cytotoxic, probably because the former halite efficiently reacts with proteins and other vitally important cellular constituents. In consequence, oxidative DNA damage and the induction of mutations and micronuclei is easily detectable at non-cytotoxic concentrations of bromate, while DNA damage by hypochlorite is observed only at cytotoxic concentrations and follows a non-linear (hockey-stick-like) dose response.

http://www.ncbi.nlm.nih.gov/pubmed/16490296

“Chronic exposures to KBrO3 cause renal cell tumors in rats, hamsters and mice and thyroid and testicular mesothelial tumors in rats.”

Toxicology • April 2006

Molecular biomarkers of oxidative stress associated with bromate carcinogenicity

Author information

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Abstract

Potassium bromate (KBrO3) is a chemical oxidizing agent found in drinking water as a disinfection byproduct of surface water ozonation. Chronic exposures to KBrO3 cause renal cell tumors in rats, hamsters and mice and thyroid and testicular mesothelial tumors in rats. Experimental evidence indicates that bromate mediates toxicological effects via the induction of oxidative stress. To investigate the contribution of oxidative stress in KBrO3-induced cancer, male F344 rats were administered KBrO3 in their drinking water at multiple concentrations for 2-100 weeks. Gene expression analyses were performed on kidney, thyroid and mesothelial cell RNA. Families of mRNA transcripts differentially expressed with respect to bromate treatment included multiple cancer, cell death, ion transport and oxidative stress genes. Multiple glutathione metabolism genes were up-regulated in kidney following carcinogenic (400 mg/L) but not non-carcinogenic (20 mg/L) bromate exposures. 8-Oxodeoxyguanosine glycosylase (Ogg1) mRNA was up-regulated in response to bromate treatment in kidney but not thyroid. A dramatic decrease in global gene expression changes was observed following 1mg/L compared to 20 mg/L bromate exposures. In a separate study oxygen-18 (18O) labeled KBrO3 was administered to male rats by oral gavage and tissues were analyzed for 18O deposition. Tissue enrichment of 18O was observed at 5 and 24 h post-KBr18O3 exposure with the highest enrichment occurring in the liver followed by the kidney, thyroid and testes. The kidney dose response observed was biphasic showing similar statistical increases in 18O deposition between 0.25 and 50 mg/L (equivalent dose) KBr18O3 followed by a much greater increase above 50 mg/L. These results suggest that carcinogenic doses of potassium bromate require attainment of a threshold at which oxidation of tissues occurs and that gene expression profiles may be predictive of these physiological changes in renal homeostasis.

http://www.ncbi.nlm.nih.gov/pubmed/16442688

“The incidence and multiplicity of renal preneoplastic lesions in rats given potassium bromate at 500 p.p.m.... were significantly higher ...”

Cancer Science • September 2006

In vivo mutagenicity and initiation following oxidative DNA lesion in the kidneys of rats given potassium bromate

Author information

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Abstract

To clarify the role of 8-OHdG formation as a starting point for carcinogenesis, we examined the dose-dependence and time-course of changes of OGG1 mRNA expression, 8-OHdG levels and in vivo mutations in the kidneys of gpt delta rats given KBrO3 in their drinking water for 13 weeks. There were no remarkable changes in OGG1 mRNA in spite of some increments being statistically significant. Increases of 8-OHdG occurred after 1 week at 500 p.p.m. and after 13 weeks at 250 p.p.m. Elevation of Spi- mutant frequency, suggestive of deletion mutations, occurred after 9 weeks at 500 p.p.m. In a two-stage experiment, F344 rats were given KBrO3 for 13 weeks then, after a 2-week recovery, treated with 1% NTA in the diet for 39 weeks. The incidence and multiplicity of renal preneoplastic lesions in rats given KBrO3 at 500 p.p.m. followed by NTA treatment were significantly higher than in rats treated with NTA alone. Results suggest that a certain period of time might be required for 8-OHdG to cause permanent mutations. The two-step experiment shows that cells exposed to the alteration of the intranuclear status by oxidative stress including 8-OHdG formation might be able to form tumors with appropriate promotion.

Full text, PDF, with graphs, charts and 46 references

http://onlinelibrary.wiley.com/doi/10.1111/j.1349-7006.2006.00248.x/epdf

“Taken together, the analysis from this study identifies potential biomarkers of exposure and illuminates a possible carcinogenic mode of action for Potassium bromate (KBrO3).”

Translational Oncogenomics • November 2006

Kidney toxicogenomics of chronic potassium bromate exposure in f344 male rats

Author information
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Rubis JA, Owen RD, Allen JW, Delker DA.

Abstract

BACKGROUND

Potassium bromate (KBrO3), used in both the food and cosmetics industry, and a drinking water disinfection by-product, is a nephrotoxic compound and rodent carcinogen. To gain insight into the carcinogenic mechanism of action and provide possible biomarkers of KBrO3 exposure, the gene expression in kidneys from chronically exposed male F344 rats was investigated.

METHODS

Male F344 rats were exposed to KBrO3 in drinking water for 52 and 100 wk. Kidneys were removed, frozen, and stored at -80°C, then used for Affymetrix microarray analysis. Gene expression patterns were examined using a non-carcinogenic (20 ppm) and carcinogenic dose (400 ppm) at 52 wk, and compared to 100 wk high dose (400 ppm) and adenoma gene expression.

RESULTS

Statistical analysis revealed 144, 224, 43, and 994 genes out of 15866 from the 52 wk low, 52 wk high, 100 wk high, and adenomas respectively, were differentially expressed when compared to control kidneys. Gene ontology classification of the 52 wk high dose showed alterations of gene transcripts involved in oxidative stress, lipid metabolism, kidney function/ion transport, and cellular function. In a comparison of kidney development gene expression, alterations were seen in the adenomas but not in the 52 wk bromate-treated kidneys. However, the normal kidney from the high dose group resembled the adenoma expression pattern with early kidney development genes being up-regulated and adult phase genes being down-regulated. Moreover, eight genes were identified which could serve as biomarkers of carcinogenic exposure to bromate. The most promising of these was Pendrin, or Slc26a4, a solute carrier of chloride and iodide active in the kidney, thyroid, and inner ear. All these tissues are targets of KBrO3 toxicity. Expression array results were verified with quantitative real-time rtPCR.

CONCLUSIONS

These data demonstrate that the 400 ppm carcinogenic dose of KBrO3 showed marked gene expression differences from the 20 ppm non-carcinogenic dose. Comparison of kidney development gene expression showed that the adenoma patterns were more characteristic of embryonic than adult kidneys, and that the normal kidney from the high dose group resembled the adenoma-like gene expression pattern. Taken together, the analysis from this study identifies potential biomarkers of exposure and illuminates a possible carcinogenic mode of action for KBrO3.

Full text, graphs, charts and 58 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3642132/

“Potassium bromate (KBrO(3)) is a by-product from ozonation of high-bromide surface water for production of drinking water and is a rodent carcinogen that produces thyroid, mesothelial, and renal tumors.”

Chemico-Biological Interactions • April 2005

Oxidative DNA damage from potassium bromate exposure in Long-Evans rats is not enhanced by a mixture of drinking water disinfection by-products

Author information

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Abstract

Public drinking water treated with chemical disinfectants contains a complex mixture of disinfection by-products (DBPs) for which the relative toxicity of the mixtures needs to be characterized to accurately assess risk. Potassium bromate (KBrO(3)) is a by-product from ozonation of high-bromide surface water for production of drinking water and is a rodent carcinogen that produces thyroid, mesothelial, and renal tumors. The proposed mechanism of KBrO(3) renal carcinogenesis involves the formation of 8-oxoguanine (8-oxoG), a promutagenic base lesion in DNA typically removed through base excision repair (BER). In this study, male Long-Evans rats were exposed via drinking water to carcinogenic concentrations of KBrO(3) (0.4 g/L), 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (0.07 g/L), chloroform (1.8 g/L), bromodichloromethane (0.7 g/L), or a mixture of all these chemicals at the same concentrations for 3 weeks. Half of one kidney was processed for microscopic examination, and the remaining kidney was frozen for isolation of genomic DNA. Levels of 8-oxoG were measured using HPLC with electrochemical detection in DNA samples incubated with formamidopyrimidine-DNA glycosylase. Aldehydic lesions (e.g. abasic sites) in DNA samples were quantitated using an aldehyde-reactive probe slot-blot assay. Treatment with KBrO(3) produced a measurable increase of 8-oxoG in the kidney, and this effect was greater than that produced by treatment with the DBP mixture. No other single chemical treatment caused measurable increases of 8-oxoG. The mixture effect on the amount of 8-oxoG observed in this study suggests an interaction between chemicals that reduced the generation of oxidative DNA damage. No increases in abasic sites were observed with treatment, but a decrease was apparent in the rats treated with the DBP mixture. These data are consistent with previous studies where chronic exposure to this chemical mixture in drinking water resulted in a less than additive carcinogenic response in Tsc2 mutant Long-Evans rats.

http://www.ncbi.nlm.nih.gov/pubmed/15840384

“Potassium bromate (KBrO3) is a prooxidant and carcinogen, inducing thyroid tumors.”

Journal Of Cellular Biochemistry • May 2005

Comparison of potential protective effects of melatonin, indole-3-propionic acid, and propylthiouracil against lipid peroxidation caused by potassium bromate in the thyroid gland

Author information

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Abstract

Potassium bromate (KBrO3) is a prooxidant and carcinogen, inducing thyroid tumors. Melatonin and indole-3-propionic acid (IPA) are effective antioxidants. Some antioxidative effects of propylthiouracil (PTU)—a thyrostatic drug—have been found. The aim of the study was to compare protective effects of melatonin, IPA, and PTU against lipid peroxidation in the thyroids, collected from rats treated with KBrO3, and in homogenates of porcine thyroids, incubated in the presence of KBrO3. Wistar rats were administered KBrO3 (110 mg/kg b.w., i.p., on the 10th day of the experiment) and/or melatonin, or IPA (0.0645 mmol/kg b.w., i.p., twice daily, for 10 days), or PTU (0.025% solution in drinking water, for 10 days). Homogenates of porcine thyroids were incubated for 30 min in the presence of KBrO3 (5 mM) plus one of the antioxidants: melatonin (0.01, 0.1, 0.5, 1.0, 5.0, 7.5 mM), or IPA (0.01, 0.1, 0.5, 1.0, 5.0, 7.5, 10.0 mM), or PTU (0.01, 0.1, 0.5, 1.0, 5.0, 7.5, 10.0 mM). The level of lipid peroxidation products (MDA + 4-HDA) was measured spectrophotometrically in thyroid homogenates. In vivo pretreatment with either melatonin or with IPA or with PTU decreased lipid peroxidation caused by KBrO3--injections in rat thyroid gland. Under in vitro conditions, PTU (5.0, 7.5, and 10.0 mM), but neither melatonin nor IPA, reduced KBrO3-related lipid peroxidation in the homogenates of porcine thyroids. In conclusion, melatonin and IPA may be of great value as protective agents under conditions of exposure to KBrO3.

http://www.ncbi.nlm.nih.gov/pubmed/15723291

“It is still of importance to investigate renal carcinogenesis by potassium bromate (KBrO3), a by-product of water disinfection by ozonation, for assessment of the risk to man. These findings suggest that DNA oxidation induced by KBrO3 may occur independently of lipid peroxidation and more than 250 ppm KBrO3 in the drinking water can exert a carcinogenic effect by way of oxidative stress.”

Cancer Science • May 2004

Dose-related changes of oxidative stress and cell proliferation in kidneys of male and female F344 rats exposed to potassium bromate

Author information

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Abstract

It is still of importance to investigate renal carcinogenesis by potassium bromate (KBrO3), a by-product of water disinfection by ozonation, for assessment of the risk to man. Five female F344 rats in each group were given KBrO3 at a dose of 300 mg/kg by single i.g. intubation or at a dose of 80 mg/kg by single i.p. injection, and were killed 48 h after the administration for measurements of thiobarbituric acid-reactive substances (TBARS) and 8-oxodeoxyguanosine (8-oxodG) levels in the kidney. Both levels in the treated animals were significantly elevated as compared with the control values. In a second experiment, 5 male and female F344 rats in each group were administered KBrO3 at concentrations of 0, 15, 30, 60, 125, 250 and 500 ppm in the drinking water for 4 weeks. KBrO3 in the drinking water did not elevate TBARS in either sex at any of the doses examined, but 8-oxodG formation in both sexes at 250 ppm and above was significantly higher than in the controls. Additionally, the bromodeoxyuridine-labeling index for proximal convoluted tubules was significantly increased at 30 ppm and above in the males, and at 250 ppm and above in the females. Alpha2u-globulin accumulation in the kidneys of male rats was increased with statistical significance at 125 ppm and above. These findings suggest that DNA oxidation induced by KBrO3 may occur independently of lipid peroxidation and more than 250 ppm KBrO3 in the drinking water can exert a carcinogenic effect by way of oxidative stress.

Full text, PDF, with graphs, charts and 45 references

http://onlinelibrary.wiley.com/doi/10.1111/j.1349-7006.2004.tb03221.x/epdf

“... cyclobutane pyrimidine dimers, CPD, and 6-pyrimidine-4-pyrimidone products, 6-4 PP), such as 8-oxodG, specifically induced by KBrO3, are likely to trigger “uncontrolled” DNA breakage in the undamaged genomic DNA ...”

Cytogenetic Genome Research • July 2004

Potassium bromate but not X-rays cause unexpectedly elevated levels of DNA breakage similar to those induced by ultraviolet light in Cockayne syndrome (CS-B) fibroblasts

Author information

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Abstract

It has been previously reported that the elevated accumulation of repair incision intermediates in cells from patients with combined characteristics of xeroderma pigmentosum complementation group D (XP-D) and Cockayne syndrome (CS) XP-D/CS fibroblasts following UV irradiation is caused by an “uncontrolled” incision of undamaged genomic DNA induced by UV-DNA-lesions which apparently are not removed. This could be an explanation for the extreme sensitivity of these cells to UV light. In the present study, we confirm the immediate DNA breakage following UV irradiation also for CS group B (CS-B) fibroblasts by DNA migration in the “comet assay” and extend these findings to other lesions such as 8-oxodeoxyguanosine (8-oxodG), selectively induced by KBrO3 treatment. In contrast, X-ray exposure does not induce differential DNA breakage. This indicates that additional lesions other than the UV-induced photoproducts (cyclobutane pyrimidine dimers, CPD, and 6-pyrimidine-4-pyrimidone products, 6-4 PP), such as 8-oxodG, specifically induced by KBrO3, are likely to trigger “uncontrolled” DNA breakage in the undamaged genomic DNA in the CS-B fibroblasts, thus accounting for some of the clinical features of these patients.

http://www.ncbi.nlm.nih.gov/pubmed/15162034

“Treatment with 4 individual disinfection by-products (DBPs), as well as a mixture of them, caused the development of aberrantcrypt foci (ACF), the putative preneoplastic lesion of colon cancer.”

[The 4 DBPs were potassium bromate, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), chloroform and bromodichloromethane individually or in a mixture]

Toxicology & Pathology • March 2003

Induction of transitional cell hyperplasia in the urinary bladder and aberrant crypt foci in the colon of rats treated with individual and a mixture of drinking water disinfection by-products

Author information

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Abstract

Cancer of the urinary bladder and colon are significant human health concerns. Epidemiological studies have suggested a correlation between these cancers and the chronic consumption of chlorinated surface water containing disinfection by-products (DBPs). The present study was designed to determine if exposure to DBPs would cause preneoplastic or neoplastic lesions in the urinary bladder and colon of rats, and what effect a mixture of DBPs would have on these lesions. Male and female Eker rats were treated via drinking water with low and high concentrations of potassium bromate, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), chloroform, or bromodichloromethane individually or in a mixture for 10 months. The urinary bladders and colons were examined for the presence of preneoplastic lesions. Cell proliferation in the urothelium was examined using immunohistochemical staining for bromodeoxyuridine. Aberrant crypt foci (ACF), as well as the number of individual crypts in each ACF, were identified and counted microscopically after staining with 0.2% methylene blue. Colon crypt cell proliferation and mitotic index were determined using immunohistochemical staining for proliferating cell nuclear antigen. Labeling indexes for the urinary bladder and colon were calculated based on the percentage of positively labeled cells. Treatment with the high dose of MX caused transitional epithelial hyperplasia and cell proliferation in the rat urinary bladder, and this effect was diminished in the high dose mixture animals. Treatment with 4 individual DBPs, as well as a mixture of them, caused the development of ACF, the putative preneoplastic lesion of colon cancer.

Full text with graphs, charts and 54 references

http://tpx.sagepub.com/content/31/2/235.long

“Potassium bromate is a potent nephrotoxic agent.
Data suggest that Nigella sativa is a potent chemopreventive agent and may suppress
Potassium bromate-mediated renal oxidative stress, toxicity and tumour promotion response ...”

Human & Experimental Toxicology • April 2003

Nigella sativa (black cumin) ameliorates potassium bromate-induced early events of carcinogenesis: diminution of oxidative stress

Author information

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Abstract

Potassium bromate (KBrO3) is a potent nephrotoxic agent. In this paper, we report the chemopreventive effect of Nigella sativa (black cumin) on KBrO3-mediated renal oxidative stress, toxicity and tumor promotion response in rats. KBrO3 (125 mg/kg body weight, intraperitoneally) enhances lipid peroxidation, gamma-glutamyl transpeptidase, hydrogen peroxide and xanthine oxidase with reduction in the activities of renal antioxidant enzymes and renal glutathione content. A marked increase in blood urea nitrogen and serum creatinine has also been observed. KBrO3 treatment also enhances ornithine decarboxylase (ODC) activity and [3H] thymidine incorporation into renal DNA. Prophylaxis of rats orally with Nigella sativa extract (50 mg/kg body weight and 100 mg/kg body weight) resulted in a significant decrease in renal microsomal lipid peroxidation ($P < 0.001$), gamma-glutamyl transpeptidase ($P < 0.001$), H2O2 ($P < 0.001$) and xanthine oxidase ($P < 0.05$). There was significant recovery of renal glutathione content ($P < 0.01$) and antioxidant enzymes ($P < 0.001$). There was also reversal in the enhancement of blood urea nitrogen, serum creatinine, renal ODC activity and DNA synthesis ($P < 0.001$). Data suggest that Nigella sativa is a potent chemopreventive agent and may suppress KBrO3-mediated renal oxidative stress, toxicity and tumour promotion response in rats.

http://www.ncbi.nlm.nih.gov/pubmed/12755470

NIGELLA SATIVA & THE NESTLE PATENT

Nigella is a genus of about 14 species of annual plants in the family Ranunculaceae, native to southern Europe, north Africa, south and southwest Asia. Common names applied to members of this genus are nigella, devil-in-a-bush or love-in-a-mist. The species grow to 20–90 cm tall, with finely divided leaves; the leaf segments are narrowly linear to threadlike. The flowers are white, yellow, pink, pale blue or pale purple, with five to 10 petals. The fruit is a capsule composed of several united follicles, each containing numerous seeds; in some species (e.g. Nigella damascena), the capsule is large and inflated. In 2010, Nestlé filed a patent application for use of extracted thymoquinone from N. sativa as a food allergy treatment. Nestlé states that the patent would cover “the specific way that thymoquinone - a compound that can be extracted from the seed of the fennel flower - interacts with opioid receptors in the body and helps to reduce allergic reactions to food.” Mainly for its seed oil extract, thymoquinone, N. sativa is under research for its potential to affect human diseases, such as cancer and dyspepsia, among others, although studies to date remain insufficient to understand its potential for clinical efficacy.

“Potassium bromate (KBrO(3)) induces DNA damage and tumors in mice and rats ...
Our results suggest that bromate is a potent mutagen ...”

Mutation Research • May 2003

Bromate induces loss of heterozygosity in the thymidine kinase gene of L5178Y/Tk(+/-)-3.7.2C mouse lymphoma cells

Author information

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Abstract

Potassium bromate (KBrO(3)) induces DNA damage and tumors in mice and rats, but is a relatively weak mutagen in microbial assays and the in vitro mammalian Hprt assay. Concern that there may be a human health risk associated with bromate, a disinfectant by-product of ozonation, has accompanied the increasing use of ozonation as an alternative to chlorination for treatment of drinking water. In this study, we have evaluated the mutagenicity of KBrO(3) and sodium bromate (NaBrO(3)) in the Tk gene of mouse lymphoma cells. In contrast to the weak mutagenic activity seen in the previous studies, bromate induced a mutant frequency of over 100 x 10(-6) at 0.6mM with minimal cytotoxicity (70-80% survival) and over 1300 x 10(-6) at 3mM (approximately 10% survival). The increase in the Tk mutant frequency was primarily due to the induction of small colony of Tk mutants. Loss of heterozygosity (LOH) analysis of 384 mutants from control and 2.7 mM KBrO(3)-treated cells showed that almost all (99%) bromate-induced mutants resulted from LOH, whereas in the control cultures 77% of the Tk mutants were LOH. Our results suggest that bromate is a potent mutagen in the Tk gene of mouse lymphoma cells, and the mechanism of action primarily involves LOH. The ability of the mouse lymphoma assay to detect a wider array of mutational events than the microbial or V79 Hprt assays may account for the potent mutagenic response.

http://www.ncbi.nlm.nih.gov/pubmed/12742504

“The results of the present investigation indicate the antioxidative effect of kolaviron, a natural antioxidant, on drug-induced [potassium bromate] kidney toxicity.”

Pharmacology Research • January 2002

Kolaviron modulates cellular redox status and impairment of membrane protein activities induced by potassium bromate (KBrO3) in rats

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Abstract

In this study, we examined the modulatory effects of kolaviron, a biflavonoid from Garcinia kola seeds on the antioxidant defense mechanisms, cellular redox status and oxidative stress in the kidney and liver of rats pretreated with potassium bromate (KBrO(3)) intragastrically as a single dose of 300 mg kg(-1)weight for 4 weeks. Treatment of rats with KBrO(3)resulted in an insignificant difference (P> 0.05) in body weight compared to controls. However, a significant increase in kidney/body weight ratio (P< 0.001) was observed in rats treated with KBrO(3)while liver/body weight ratio was not affected. KBrO(3)depressed the activities of superoxide dismutase, glutathione peroxidase and catalase (P< 0.001) in the kidney but not in the liver. Kolaviron (200 mg kg(-1)body weight) administered three times a week for 4 weeks inhibited the decrease mediated by KBrO(3)of these enzymes in the kidney by 29, 88 and 45%, respectively. Similarly, kolaviron reduced the KBrO(3)-induced decrease in the activities of gamma -glutamyltransferase and microsomal Ca(2+)ATPase by 73 and 63% in the kidney. In addition, the extract elicited a 27 and 25% decrease in the KBrO(3)-induced increase in malondialdehyde and lipid hydroperoxide formation in the kidney. Kolaviron also attenuated the KBrO(3)-decreased activities of glucose 6-phosphatase, 5 prime prime or minute nucleotidase and alkaline phosphatase (membrane enzymes) by 72, 57 and 25% respectively. The results of the present investigation indicate the antioxidative effect of kolaviron, a natural antioxidant, on drug-induced kidney toxicity. Kolaviron may therefore intervene in the cellular redox status and depression of membrane protein activities caused by KBrO(3) and other environmental carcinogens in the kidney.

http://www.ncbi.nlm.nih.gov/pubmed/11820864

KOLAVIRON EXTRACT AND GARCINIA SEEDS

Garcinia is a plant genus native to Asia, Australia, tropical and southern Africa, and Polynesia. The number of species is highly disputed, with various sources recognizing between 50 and about 300. Commonly, the plants in this genus are called saptrees, mangosteens (which may also refer specifically to the purple mangosteen, G. mangostana), garcinias or, ambiguously, “monkey fruit”. Many species are threatened by habitat destruction, and at least G. cadelliana from South Andaman Island is almost or even completely extinct already. The fruits are a food source for several animals, such as the archduke butterflies (Lexias) of tropical eastern Asia which relish the sap of overripe mangosteens. Garcinia species are evergreen trees and shrubs. The fruit is a berry with fleshy endocarp, which in several species is delicious.

“Clear cell renal tumors, the most common form of human renal epithelial neoplasm, are rare in animals but are inducible by potassium bromate in F344 rats. Potassium bromate-induced rat renal tumors are morphologically similar to their human counterpart but the genetic basis of tumorigenesis is different.”

Cancer Letters • December 2002

Mutations in the VHL gene from potassium bromate-induced rat clear cell renal tumors

Author information

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Abstract

Potassium bromate (KBrO(3)) is a rat renal carcinogen and a major drinking water disinfection by-product in water disinfected with ozone. Clear cell renal tumors, the most common form of human renal epithelial neoplasm, are rare in animals but are inducible by KBrO(3) in F344 rats. Detection of cytoplasmic periodic acid-Schiff-positive granules in clear cell tumors, indicative of glycogen accumulation, provides evidence of their biochemical similarity to human counterparts. Mutation in the coding region of the von Hippel-Lindau (VHL) gene is frequently detected in human clear cell renal carcinomas. Detection of VHL mutations in KBrO(3)-induced rat renal tumors could enhance the relevancy of these rat renal tumors for human health risk assessment. Formalin-fixed paraffin-embedded control tissues and renal tumors from male F344 rats exposed to KBrO(3) in the drinking water for 2 years were examined microscopically and were microdissected for DNA extraction. The coding sequence and a promoter region of the VHL gene were examined by polymerase chain reaction-single strand conformation polymorphism and/or DNA sequencing. Two of nine clear cell renal tumors carried the same C to T mutation at the core region of the Sp1 transcription factor binding motif in the VHL promoter and one of four untreated animals had C to T mutation outside the highly conserved core region. Mutation in the VHL coding sequence was only detected in one tumor. No VHL mutations were observed in three chromophilic tumors. KBrO(3)-induced rat renal tumors are morphologically similar to their human counterpart but the genetic basis of tumorigenesis is different.

http://www.ncbi.nlm.nih.gov/pubmed/12359370

Toxicology And Applied Pharmacology • December 2001

Toxic effects of potassium bromate and thioglycolate on vestibuloocular reflex systems of Guinea pigs and humans

Author information
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“Potassium bromate (KBrO3) and thioglycolate are two components of hair curling solution. Our clinical findings together with the animal study imply that clinicians should be alert to the risk of bromate exposure in hairdressers, especially those with vertigo, tinnitus, or hearing loss.”

Abstract

Potassium bromate (KBrO(3)) and thioglycolate are two components of hair curling solution. The neurotoxic effects of KBrO(3) and thioglycolate on the vestibuloocular reflex (VOR) system have not been elucidated. In this paper, we report the adverse effects of KBrO(3) and thioglycolate on the VOR system of Hartley-strain guinea pigs. The function of the VOR system was evaluated by caloric test coupled with the electronystagmographic recordings after subcutaneous injection of 20 or 50 mg/kg KBrO(3) or 15 mg/kg thioglycolate, either alone or in combination once daily for 14 consecutive days. The results showed that KBrO(3) produced abnormal caloric responses in a concentration-dependent manner and thioglycolate enhanced this abnormality. Our clinical patients, 10 female hairdressers exposed to the hair curling solution for 10-30 years revealed a similar dysfunction in the caloric test. The possible mechanism of this adverse effect was studied: the cerebellar-regulated functions such as motor equilibrium performance and spontaneous locomotor activity of guinea pigs were reduced, the enzymatic Na(+)/K(+)-ATPase and Ca(2+)-ATPase activities of cerebellar tissues were significantly decreased, and the loss of Purkinje cells as well as the derangement of the granular cell layer of the cerebellar cortex was revealed after treatment with KBrO(3) plus thioglycolate. These findings imply that KBrO(3) plus thioglycolate is toxic to the VOR system, mediated by, at least in part, the dysfunction of a higher cerebellar regulatory mechanism. We suggest that the caloric test is a noninvasive method for monitoring the consequences of hazardous exposure of hair curling solution in humans. Our clinical findings together with the animal study imply that clinicians should be alert to the risk of bromate exposure in hairdressers, especially those with vertigo, tinnitus, or hearing loss.

http://www.ncbi.nlm.nih.gov/pubmed/11740909

Toxicology & Pathology • March 2000

Origin and distribution of potassium bromate-induced testicular and peritoneal mesotheliomas in rats

Author information

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Abstract

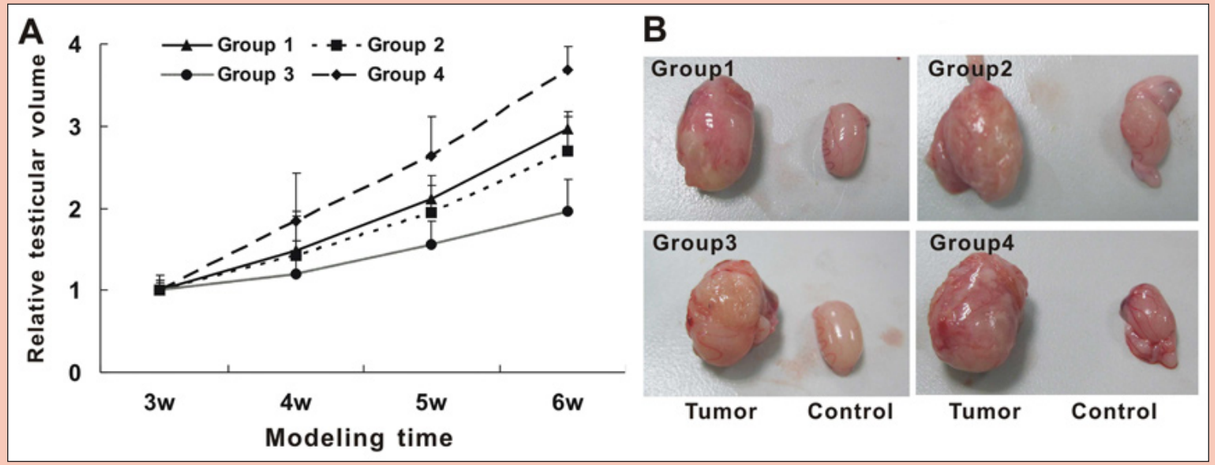
Tissue sections were examined from a 2-year bioassay of male Fischer 344 rats treated with potassium bromate administered in drinking water. All animals exhibiting peritoneal mesotheliomas also had mesotheliomas of the tunica vaginalis testis mesorchium (the reverse was not true), and the correlation of these 2 types of mesotheliomas was highly significant (r2 = 0.98). Mapping of the tunica vaginalis tumors at all time points and at all bromate concentrations revealed a pattern of increasing incidence of tumor formation on the mesothelium of the tunica vaginalis testis as a function of proximity to the mesorchial ligament. Thus, the mesorchium appears to be the major mesothelial target site for potassium bromate-mediated carcinogenesis. The frequency of occurrence of mesotheliomas by location was tunica vaginalis testis (25%), mesosplenium (20%), mesentery (10%), mesojejunum/mesocolon (8%), bladder (6.5%), mesogastrium (13%), liver serosa (5%), and kidney, small intestine, and rectum (1% each). A complete cross-section of the rat testis was prepared and used to construct a complete map of the mesothelium. Any attempt to determine the role of local dose and tissue susceptibility for the purpose of interspecies risk extrapolation must take into account the complex anatomy and physiology of this region of the visceral and testicular suspensory apparatus. Improved histologic approaches are needed for adequate assessment of this delicate suspensory system.

Full text with graphs, charts and 24 references

http://tpx.sagepub.com/content/28/2/253.long

MESORCHIUM

The testes, at an early period of fetal life, are placed at the back part of the abdominal cavity, behind the peritoneum, and each is attached by a peritoneal fold called the mesorchium.



“Potassium bromate (KBrO3) is known to be an oxidizing agent that is used not only as a food additive, mainly in the bread-making process, but also as a neutralizer in thioglycolate containing hair curling set ... it has been shown that bromate poisoning could cause severe and irreversible sensorineural hearing loss as well as renal failure ...”

Chinese Journal Of Physiology • June 2000

The detrimental effects of potassium bromate and thioglycolate on auditory brainstem response of guinea pigs

Author information

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Abstract

Potassium bromate (KBrO3) is known to be an oxidizing agent that is used not only as a food additive, mainly in the bread-making process, but also as a neutralizer in thioglycolate containing hair curling set. Although it has been shown that bromate poisoning could cause severe and irreversible sensorineural hearing loss as well as renal failure, the action mechanism of bromate-induced otoneurotoxicity especially its combination with thioglycolate remains to be studied. In this study, we attempted to investigate the toxic effects of KBrO3 in combination with or without thioglycolate on the auditory brainstem response (ABR) system in the guinea-pigs which was claimed to be very susceptible to the xenobiotics. In a preliminary test, we have found that after consecutive 2 weeks administration, KBrO3 caused a significant prolongation of wave I-III and the interwave latencies of ABR as well as significantly elevated the threshold of hearing, suggesting that the conduction velocity of the peripheral auditory nerve was delayed. By contrast, the absolute latency of wave IV/V and the interwave latency of wave III-V were not significantly prolonged, suggesting that KBrO3 had no effect on the brainstem. This oto-neurotoxic effect of KBrO3 was markedly enhanced by combining with thioglycolate. Our data also indicated that KBrO3 combined with thioglycolate but not KBrO3 alone prominantly caused a decrease of body weight. However, enzymatic activities (including Na+/K+-ATPase and Ca2+-ATPase) and the level of nitric oxide (NO) was significantly affected in the brainstem. Based on these findings, we tentatively conclude that whether KBrO3 alone or KBrO3 combined with thioglycolate induced oto-neurotoxicity majorly through the peripheral auditory nerve rather than via the central brainstem intoxication.

http://www.ncbi.nlm.nih.gov/pubmed/10994699

“We have investigated the role of reduced glutathione in the genetic toxicity of the rodent renal carcinogen potassium bromate. DNA strand breakage was also induced by potassium bromate in human white blood cells and rat kidney epithelial cells.”

Mutagenesis • July 2000

The role of glutathione in DNA damage by potassium bromate in vitro

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Abstract

We have investigated the role of reduced glutathione (GSH) in the genetic toxicity of the rodent renal carcinogen potassium bromate (KBrO(3)). A statistically significant increase in the concentration of 8-oxodeoxyguanosine (8-oxodG) relative to deoxyguanosine was measured following incubation of calf thymus DNA with KBrO(3) and GSH or N-acetylcysteine (NACys). This was dependent on these thiols and was associated with the loss of GSH and production of oxidized glutathione. A short-lived (<6 min) intermediate was apparent which did not react with the spin trap dimethylpyrroline N-oxide. DNA oxidation was not evident when potassium chlorate (KClO(3)) or potassium iodate (KIO(3)) were used instead of KBrO(3), though GSH depletion also occurred with KIO(3), but not with KClO(3). Other reductants and thiols in combination with KBrO(3) did not cause a significant increase in DNA oxidation. DNA strand breakage was also induced by KBrO(3) in human white blood cells (5 mM) and rat kidney epithelial cells (NRK-52E, 1.5 mM). This was associated with an apparent small depletion of thiols in NRK-52E cells at 15 min and with an elevation of 8-oxodG at a delayed time of 24 h. Depletion of intra-cellular GSH by diethylmaleate in human lymphocytes decreased the amount of strand breakage induced by KBrO(3). Extracellular GSH, however, protected against DNA strand breakage by KBrO(3), possibly due to the inability of the reactive product to enter the cell. In contrast, membrane-permeant NACys enhanced KBrO(3)-induced DNA strand breakage in these cells. DNA damage by KBrO(3) is therefore largely dependent on access to intracellular GSH.

Full text with graphs, charts and 36 references

http://mutage.oxfordjournals.org/content/15/4/311.long

“Many chemical compounds which induce oxidative stress in the tissue produce carcinogenesis either alone or act as a tumor promoter in carcinogen-initiated animals after prolonged exposure. Here, we report that potassium bromate induces renal proliferative response and damage by elaborating oxidative stress. These results suggest that oxidant generating potassium bromate acts as a potent proliferator of kidney and acts by producing oxidative damage.”

Cancer Letters • January 1999

Potassium bromate (KBrO3) induces renal proliferative response and damage by elaborating oxidative stress

Author information
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Abstract

Many chemical compounds which induce oxidative stress in the tissue produce carcinogenesis either alone or act as a tumor promoter in carcinogen-initiated animals after prolonged exposure. Here, we report that potassium bromate (KBrO3) induces renal proliferative response and damage by elaborating oxidative stress. KBrO3 administration dose dependently induced renal ornithine decarboxylase (ODC) activity several fold compared to its activity in saline-treated rats. Similarly renal DNA synthesis which has been measured as [3H]thymidine incorporation in DNA also increases. KBrO3 administration also depleted the level of renal glutathione and glutathione reductase activity in a time dependent manner. The maximum depletion in the levels of renal glutathione and glutathione reductase activity was observed 3 h after KBrO3 treatment which was 60 and 40%, respectively, of saline-treated controls. Parallel to these changes, a sharp increase in the blood urea nitrogen and serum creatinine levels was observed which is indicative of the concurrent renal damage. These results suggest that oxidant generating KBrO3 acts as a potent proliferator of kidney and acts by producing oxidative damage.

http://www.ncbi.nlm.nih.gov/pubmed/10096427

“The genotoxic potential of two oxidizing compounds, potassium bromate and potassium superoxide, was comparatively tested in various genotoxicity tests ... Our results suggest that the two oxidizing compounds induce specific patterns of genotoxic effects that reflect the types of DNA alterations induced ...”

Mutation Research • February 1999

Comparative evaluation of the genotoxic properties of potassium bromate and potassium superoxide in V79 Chinese hamster cells

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Abstract

The genotoxic potential of two oxidizing compounds, potassium bromate and potassium superoxide, was comparatively tested in various genotoxicity tests with V79 Chinese hamster cells. Both substances clearly induced cytotoxicity, chromosome aberrations and increased DNA migration in the alkaline comet assay. Using a modified comet assay protocol with FPG protein, a DNA repair enzyme which specifically nicks DNA at sites of 8-oxoguanines and formamidopyrimidines, we detected oxidative DNA base damage only after potassium bromate treatment. HPLC analysis also revealed significantly increased levels of 8-oxodeoxyguanosine after potassium bromate treatment but not after potassium superoxide treatment. Furthermore, potassium bromate clearly induced gene mutations at the HPRT locus while potassium superoxide only had a small effect on HPRT mutant frequencies. Molecular analysis of potassium bromate-induced mutations indicated a high portion of deletion mutations. Three out of four point mutations were G to T transversions which typically arise after replication of 8-oxoguanine. Our results suggest that the two oxidizing compounds induce specific patterns of genotoxic effects that reflect the types of DNA alterations induced by different reactive oxygen species (ROS).

http://www.ncbi.nlm.nih.gov/pubmed/10023063

“The present study showed that potassium bromate (KBrO3) is carcinogenic in the rat kidney, thyroid, and mesothelium and is a renal carcinogen in the male mouse, potassium bromate (KBrO3) was carcinogenic in rodents at water concentrations as low as 0.02 g/L (20 ppm; 1.5 mg/kg/day). These data can be used to estimate the human health risk that would be associated with changing from chlorination to ozonation for disinfection of drinking water.”

Toxicology & Pathology • September 1998

Carcinogenicity of potassium bromate administered in the drinking water to male B6C3F1 mice and F344/N rats

Author information

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Abstract

Ozone has been proposed for water disinfection because it is more efficient than chlorine for killing microbes and results in much lower levels of carcinogenic trihalomethanes than does chlorination. Ozone leads to formation of hypobromous acid in surface waters with high bromine content and forms brominated organic by-products and bromate. The carcinogenicity and chronic toxicity of potassium bromate (KBrO3) was studied in male B6C3F1 mice and F344/N rats to confirm and extend the results of previous work. Mice were treated with 0, 0.08, 0.4, or 0.8 g/L KBrO3 in the drinking water for up to 100 wk, and rats were provided with 0, 0.02, 0.1, 0.2, or 0.4 g/L KBrO3. Animals were euthanatized, necropsied, and subjected to a complete macroscopic examination. Selected tissues and gross lesions were processed by routine methods for light microscopic examination. The present study showed that KBrO3 is carcinogenic in the rat kidney, thyroid, and mesothelium and is a renal carcinogen in the male mouse, KBrO3 was carcinogenic in rodents at water concentrations as low as 0.02 g/L (20 ppm; 1.5 mg/kg/day). These data can be used to estimate the human health risk that would be associated with changing from chlorination to ozonation for disinfection of drinking water.

Full text with graphs, charts and 55 references: http://tpx.sagepub.com/content/26/5/587.long

“Potassium bromate (KBrO3) is a rodent carcinogen and a nephrotoxicant and neurotoxicant in humans. KBrO3 was dissolved in drinking water at nominal concentrations of 0, 0.02, 0.1, 0.2, and 0.4 g/L and administered to male F344 rats as the sole water source for 12, 26, 52, 78, or 100 wk. Renal cell tumors were present after 52 wk of treatment only in the high-dose group. Mesotheliomas developed after 52 wk of treatmenton the tunica vaginalis. Mesotheliomas were present at sites other than the testicle after 78 wk of treatment, indicating that their origin was the testicular tunic. Thyroid follicular tumors were present as early as 26 wk in 1 rat each from the 0.1- and 0.2-g/L groups.”

Toxicology & Pathology • November 1998

Time- and dose-dependent development of potassium bromate-induced tumors in male Fischer 344 rats

Author Information

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Abstract

Potassium bromate (KBrO3) is a rodent carcinogen and a nephro- and neurotoxicant in humans. KBrO3 is used in cosmetics and food products and is a by-product of water disinfection by ozonization. KBrO3 is carcinogenic in the rat kidney, thyroid, and mesothelium and is a renal carcinogen in the male mouse. The present study was designed to investigate the relationship of time and dose to bromate-induced tumors in male Fischer 344 (F344) rats and to provide some insight into the development of these tumors. KBrO3 was dissolved in drinking water at nominal concentrations of 0, 0.02, 0.1, 0.2, and 0.4 g/L and administered to male F344 rats as the sole water source for 12, 26, 52, 78, or 100 wk. Renal cell tumors were present after 52 wk of treatment only in the high-dose group. Mesotheliomas developed after 52 wk of treatment on the tunica vaginalis. Mesotheliomas were present at sites other than the testicle after 78 wk of treatment, indicating that their origin was the testicular tunic. Thyroid follicular tumors were present as early as 26 wk in 1 rat each from the 0.1- and 0.2-g/L groups. The present study can be used as a basis for the determination of dose-time relationships of tumor development for a better understanding of KBrO3-induced cancer.

Full text with graphs, charts and 30 references

http://tpx.sagepub.com/content/26/6/724.long

“This ‘damage profile’ ... excluded the involvement of hydroxyl radicals and single oxygen in the damage production, but were consistent with a radical mechanism involving bromine radicals.”

Carcinogenesis • February 1995

Oxidative DNA damage induced by potassium bromate under cell-free conditions and in mammalian cells

Author information
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Abstract

The oxidative DNA damage induced by the renal carcinogen potassium bromate (KBrO3) in cultured mammalian cells and in a cell-free system was characterized by means of various repair endonucleases. Under cell-free conditions, no modifications were induced by KBrO3 alone, but extensive DNA damage was observed in the presence of glutathione (GSH). The DNA damage was found to consist mostly of base modifications sensitive to Fpg protein (formamidopyrimidine-DNA glycosylase). HPLC analysis demonstrated that many of the modifications were 7,8-dihydro-8-oxoguanine(8-hydroxyguanine) residues. Single-strand breaks, sites of base loss (AP sites) and base modifications sensitive to endonuclease III (5,6-dihydropyrimidine derivatives) were formed in only low amounts. This ‘damage profile’ and experiments with various scavengers (catalase, superoxide dismutase, deferoxamine, azide, tert-butanol) and D2O as solvent excluded the involvement of hydroxyl radicals and single oxygen in the damage production, but were consistent with a radical mechanism involving bromine radicals. In L1210 mouse leukemia cells and LLC-PK1 porcine kidney cells, KBrO3 alone gave rise to a DNA damage profile similar to that observed after treatment of cell-free DNA with KBrO3 plus GSH, i.e. base modifications sensitive to Fpg protein were formed in high excess of all other lesions quantified. In LLC-PK1 cells (derived from the target organ of KBrO3-induced carcinogenesis) the level of DNA damage was twice that in the L1210 cells. DNA damage was partially prevented by depletion of intracellular GSH with diethylmaleate, indicating that GSH played an activating role in the cells similar to that seen under cell-free conditions. The Fpg-sensitive base modifications induced by KBrO3 were repaired with only moderate efficiency (38 +/- 10% of the lesions were still present after 18 h in full medium) under conditions that did not influence cell proliferation.

http://www.ncbi.nlm.nih.gov/pubmed/7859366

“The overall data suggest that oxidative stress generated by KBrO3 exposure might be associated with induction of cell proliferation and associated [cancer] promoting activity.”

Carcinogenesis • March 1995

A possible role for oxidative stress in potassium bromate (KBrO3) carcinogenesis

Author information

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Abstract

In order to clarify the role of oxidative stress in carcinogenesis by potassium bromate (KBrO3), 8-hydroxydeoxyguanosine (8-OH-dG) levels and cumulating replicating fractions (CRFs) were measured in the kidneys and livers of F344 rats receiving gavage doses of 100, 200 or 400 mg/kg. We used female rats in this study to allow the potential of KBrO3 for inducing alpha 2u-globulin accumulation—known to result in sustained cell proliferation and eventual promoting activity in males—to be ignored. Additional female rats were given 0.05% N-ethyl-N-hydroxyethylnitrosamine (EHEN) orally for the first 2 weeks as an initiator with subsequent administration of KBrO3 at a dose of 500 p.p.m. in the drinking water for 30 weeks. 8-OH-dG levels in the kidneys were significantly elevated with doses of 200 and 400 mg/kg, and this correlated with increases of the CRFs of proximal tubules. In the livers, however, no significant changes were found. In the promotion bioassay, the mean numbers of atypical tubules, atypical hyperplasias and renal cell tumors per rat in animals treated with KBrO3 after EHEN initiation were significantly higher than those in animals receiving distilled water after EHEN initiation. In contrast, there were no significant differences between groups in terms of liver tumors. The overall data suggest that oxidative stress generated by KBrO3 exposure might be associated with induction of cell proliferation and associated promoting activity.

http://www.ncbi.nlm.nih.gov/pubmed/7697818

“These findings provide support for involvement of lipid peroxidation in producing oxidized DNA damage by potassium bromate directly to renal proximal tubules, the target site for renal carcinogenesis.”

Cancer Letters • November 1994

Oxidative DNA damage induced by potassium bromate in isolated rat renal proximal tubules and renal nuclei

Author information

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Dabbs JE, Hasegawa R, Kurokawa Y.
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Abstract

Oxidative damage caused by potassium bromate (KBrO3), a rat renal carcinogen, was investigated using in vitro preparations of rat renal proximal tubules (RPT) and renal nuclear fractions. Release of lactate dehydrogenase and decrease of SH-group content in RPT (1 mg protein/ml) by KBrO3 (0.5-5 mM) in a concentration- and time-dependent manner were observed. Peroxidized arachidonic acid and 8-hydroxydeoxyguanosine (8-OH-dG) levels in RPT were increased after administration of 2 and 5 mM KBrO3. 8-OH-dG formation was observed after incubation of renal nuclei with a lipid-peroxiding system, autooxidized methyl linolenate, or KBrO3. These findings provide support for involvement of lipid peroxidation in producing oxidized DNA damage by KBrO3 directly to RPT, the target site for renal carcinogenesis.

http://www.ncbi.nlm.nih.gov/pubmed/7954362

“Considering the fact that potassium bromate has genotoxic potential involving oxidative stress, we hypothesize that the induced cell proliferation might predominantly play an additive role in its carcinogenesis.”

Journal Of Cancer Research And Clinical Oncology • May 1993

A possible role for cell proliferation in potassium bromate (KBrO3) carcinogenesis

Author information

Umemura T1, Sai K, Takagi A, Hasegawa R, Kurokawa Y.

Division of Toxicology, National Institute of Health Sciences, Tokyo, Japan

Abstract

Accumulation of alpha 2u-globulin and induction of cell proliferation were examined in kidneys of rats exposed to KBrO3, KBr or NaBrO3 in their drinking water. Hyaline droplets observed after KBrO3 or NaBrO3 administration to male rats were specifically immunostained for alpha 2u-globulin. Increases in cell proliferation were found in the proximal tubules of male rats given KBrO3 or NaBrO3 but not KBr for 2, 4, and 8 weeks. No such change was evident in KBrO3-treated female rats or the distal tubules of any treated animal. The concordance between hyaline droplet accumulation and increased cell turnover suggests that KBrO3- and NaBrO3-induced cell replication in kidneys of male rats may result from alpha 2u-globulin nephropathy. Considering the fact that KBrO3 has genotoxic potential involving oxidative stress, we hypothesize that the induced cell proliferation might predominantly play an additive role in its carcinogenesis. Furthermore, the present data, showing similar effects of NaBrO3 on the rat kidney, are of direct significance to its risk assessment.

http://www.ncbi.nlm.nih.gov/pubmed/7685357

“The results showed that seven genotoxic and nine non-genotoxic [food] chemicals promoted cell aging.”

Abstract

The potency of food chemicals to induce cell aging was evaluated in human diploid fibroblast cells HAIN-55 having a finite replicative potential by using in vitro aging markers, i.e., decreases of maximum proliferative potential (lifespan) of cells, saturation density in monolayer culture (SD), plating efficiency (PE) and mitotic index (MI), and an increase of cells with polyploid karyotypes. By treatment twice with low concentration of genotoxic chemicals aflatoxin B1, allylisothiocyanate or trans-cinnamaldehyde (severe clastogenic flavoring agent; Kasamaki et al., 1982), lifespan (expressed by the number of cumulative cell population doubling (CPD)) of the treated cells was reduced by 8-12 CPDs accompanied by change of the other aging markers. By successive treatment (29 or 25 times) with non-genotoxic chemical aspartame (N-L-aspartyl-L-phenylalanine) or L-canavanine (structural analogue of L-arginine), lifespan of the treated cells was also slightly shortened (by 2-6 CPDs) compared with the untreated control cells. In the process of cell aging, Mitochondrial activity (MTT activity) decreased almost in parallel with the decrease of SD and MI. On the basis of these results, a variety of genotoxic and non-genotoxic chemicals were examined by using MTT activity as the aging marker for their effects on the aging of HAIN-55 cells and bovine artery endothelial cells which also had a finite replicative potential. The results showed that seven genotoxic and nine non-genotoxic chemicals promoted cell aging.

Journal Of Toxicology Science • August 1993

The effect of food chemicals on cell aging of human diploid cells in in-vitro culture

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http://www.ncbi.nlm.nih.gov/pubmed/8246307

Regulatory Toxicology And Pharmacology • April 1990

Regulation of food-related carcinogens in Japan

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Toyama Institute of Health, Japan.

Abstract

“Use of hazardous environmental substances in Japan is regulated, based on their risk assessment, by laws of various ministries, depending upon the chemicals concerned. Food additives and food contaminants are controlled by the Food Sanitation Law of the Ministry of Health and Welfare. When manufacture or import of new food additives is intended, their physicochemical and biological data are evaluated by the Food Sanitation Investigation Council. When new data become available on the carcinogenicity of food additives that have been approved and are in use, these compounds are reevaluated. Between 1974 and 1986, twelve chemicals were proved to be carcinogenic in Japan by task groups for evaluation of the carcinogenicity of food additives, medical drugs and pesticides, which were organized by the Ministry of Health and Welfare. Of these compounds, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide was banned from use, but use of hydrogen peroxide and potassium bromate was permitted, provided that these compounds were decomposed or removed from the final products. The use of butylated hydroxyanisole within fixed limits in some foodstuffs was also permitted. Decisions on the use of these compounds were based on the prevailing opinion on carcinogens at the time. This paper reports these facts with a consideration of future problems on the regulation of food carcinogens.”

http://www.ncbi.nlm.nih.gov/pubmed/2185510

“It has been demonstrated that Potassium bromate induces renal cell tumors, mesothliomas of the peritoneum, and follicular cell tumors of the thyroid. In addition, experiments aimed at elucidating the mode of carcinogenic action have revealed that Potassium bromate is a complete carcinogen, possessing both initiating and promoting activities ...”

Environmental Health Perspectives • July 1990

Toxicity and carcinogenicity of potassium bromate—a new renal carcinogen

By Y Kurokawa, A Maekawa, M Takahashi, and Y Hayashi

Division of Toxicology, National Institute of Hygienic Sciences, Tokyo, Japan

Abstract

Potassium bromate (KBrO3) is an oxidizing agent that has been used as a food additive, mainly in the bread-making process. Although adverse effects are not evident in animals fed bread-based diets made from flour treated with KBrO3, the agent is carcinogenic in rats and nephrotoxic in both man and experimental animals when given orally. It has been demonstrated that KBrO3 induces renal cell tumors, mesotheliomas of the peritoneum, and follicular cell tumors of the thyroid. In addition, experiments aimed at elucidating the mode of carcinogenic action have revealed that KBrO3 is a complete carcinogen, possessing both initiating and promoting activities for rat renal tumorigenesis. However, the potential seems to be weak in mice and hamsters. In contrast to its weak mutagenic activity in microbial assays, KBrO3 showed relatively strong potential inducing chromosome aberrations both in vitro and in vivo. Glutathione and cysteine degrade KBrO3 in vitro; in turn, the KBrO3 has inhibitory effects on inducing lipid peroxidation in the rat kidney. Active oxygen radicals generated from KBrO3 were implicated in its toxic and carcinogenic effects, especially because KBrO3 produced 8-hydroxydeoxyguanosine in the rat kidney. A wide range of data from applications of various analytical methods are now available for risk assessment purposes.

Full text, PDF, graphs, charts with 111 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1567851/

“Five compounds, i.e. chlorine dioxide, maltol, potassium bromate, sodium chlorite and sodium dehydroacetate, were found to induce micronuclei after a single ip injection. Potassium bromate, sodium chlorite and sodium dehydroacetate were tested further by oral administration, and potassium bromate showed a clearly positive result.”

Food Chemistry & Toxicology • June 1988

Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals

Author information

Hayashi M1, Kishi M, Sofuni T, Ishidate M Jr.
Biological Safety Research Center, National Institute of Hygienic Sciences, Tokyo, Japan

Abstract

A total of 47 chemical substances including 32 synthetic food additives, seven additives from natural sources, three trihalogenated methanes, two fluoro-compounds for dental use, one insecticide, and two other compounds were subjected to the micronucleus test in mice. Five compounds, i.e. chlorine dioxide, maltol, potassium bromate, sodium chlorite and sodium dehydroacetate, were found to induce micronuclei after a single ip injection. Potassium bromate, sodium chlorite and sodium dehydroacetate were tested further by oral administration, and potassium bromate showed a clearly positive result. Almost all the compounds which were negative with the single treatment were additionally tested by four or five multiple treatments, but none showed any indication of micronucleus induction.

http://www.ncbi.nlm.nih.gov/pubmed/3169648

“Renal cell adenomas were found as early as after 26 weeks of treatment with potassium bromate (KBrO3). The yields of dysplastic foci, adenomas and adenocarcinomas of the kidney, follicular cell tumors of the thyroid and mesotheliomas of the peritoneum increased with treatment, the final incidences all being statistically significant after administration of KBrO3 for 104 weeks.”

Japanese Journal Of Cancer Research • April 1987

Relationship between the duration of treatment and the incidence of renal cell tumors in male F344 rats administered potassium bromate

Kurokawa Y, Matsushima Y, Takamura N, Imazawa T, Hayashi Y.

Abstract

In order to ascertain the minimum induction time, minimum treatment period and total dose required for development of renal cell tumors, KBrO3 at a concentration of 500 ppm was administered in the drinking water to a total of 232 male F344 rats divided into 14 experimental groups and the development of tumors was examined by two different approaches. In a continued-treatment study, administration of KBrO3 was stopped at week 13, 26, 39, 52 or 104 and rats were immediately sacrificed for comparison with controls given distilled water (DW) alone. Renal cell adenomas were found as early as after 26 weeks of treatment with KBrO3. The yields of dysplastic foci, adenomas and adenocarcinomas of the kidney, follicular cell tumors of the thyroid and mesotheliomas of the peritoneum increased with treatment, the final incidences all being statistically significant after administration of KBrO3 for 104 weeks. To examine the effect of discontinued treatment, on the other hand, the rats were given KBrO3 for the first 13, 26, 39 or 52 weeks and were subsequently maintained on DW alone until sacrifice at week 104. The incidences of tumors in these groups were compared with that of a group continuously administered KBrO3 for 104 weeks. The yields of renal dysplastic foci, adenomas and adenocarcinomas in all discontinued-treatment groups were approximately equal to or even higher than those in the group given KBrO3 continuously for 104 weeks. It is concluded that, under the conditions of this study: the minimum induction time for the development of renal adenomas was 26 weeks and the minimum treatment period and total dose for the induction of renal adenomas and adenocarcinomas were 13 weeks and 4 g/kg, respectively, when the rats were maintained thereafter on DW for 2 years.

http://www.ncbi.nlm.nih.gov/pubmed/3108216

Journal Of The National Cancer Institute • October 1986

Dose-response studies on the carcinogenicity of potassium bromate in F344 rats after long-term oral administration

Kurokawa Y, Aoki S, Matsushima Y, Takamura N, Imazawa T, Hayashi Y.

Abstract

Dose-response studies on the carcinogenicity of potassium bromate (KBrO3), a food additive, were undertaken to examine its effects at low doses. A total of 148 6-week-old male inbred F344 rats were divided into 7 groups. They were given KBrO3 orally in their drinking water at doses of 500, 250, 125, 60, 30, 15, and 0 ppm for 104 weeks, at the end of which time all the surviving animals were autopsied and then examined histopathologically. Shortening of the survival times and marked inhibition of body weight increase were observed in a group given 500 ppm KBrO3. The combined incidences of renal adenocarcinomas and adenomas were significantly increased in rats treated with KBrO3 at doses of 500, 250, and 125 ppm in a dose-related manner. The dose-response curve showed a sigmoid appearance. The value for the virtually safe dose (VSD), calculated by the probit model, was 0.950 ppm KBrO3 at a risk level of 10(-6). However, significant increases in the occurrence of dysplastic foci of the kidney were found in groups at doses higher than 30 ppm KBrO3. The VSD value for the dysplastic foci estimated by the gamma-multi-hit model was 0.148 X 10(-3) ppm KBrO3 at a risk level of 10(-6). In a group tested with 500 ppm KBrO3, the combined incidences for follicular adenocarcinomas and adenomas of the thyroid and for mesotheliomas of the peritoneum were shown to be significantly increased.

http://www.ncbi.nlm.nih.gov/pubmed/3463824

“Dose-response studies on the carcinogenicity of potassium bromate (KBrO3), a food additive, were undertaken to examine its effects at low doses. Shortening of the survival times and marked inhibition of body weight increase were observed in a group given 500 ppm KBrO3. The combined incidences of renal adenocarcinomas and adenomas were significantly increased in rats treated with KBrO3 at doses of 500, 250, and 125 ppm in a dose-related manner. The value for the virtually safe dose (VSD), calculated by the probit model, was 0.950 ppm KBrO3 ... a group tested with 500 ppm KBrO3, the combined incidences for follicular adenocarcinomas and adenomas of the thyroid and for mesotheliomas of the peritoneum were shown to be significantly increased.”

“We concluded that KBrO3 was carcinogenic in rats of both sexes.”

Environmental Health Perspectives • November 1986

Long-term in vivo carcinogenicity tests of potassium bromate, sodium hypochlorite, and sodium chlorite conducted in Japan

Kurokawa Y, Takayama S, Konishi Y, Hiasa Y,
Asahina S, Takahashi M, Maekawa A, Hayashi Y.

Abstract

Long-term in vivo carcinogenicity tests of potassium bromate (KBrO3), sodium hypochlorite (NaClO), and sodium chlorite (NaClO2) have been conducted in Japan from 1977 to 1985. In these investigations, groups of approximately 50 male and 50 female F344 rats or B6C3F1 mice were given solutions of the compounds as their drinking water ad libitum at two dose levels determined on the basis of preliminary 13-week tests. Control animals were given distilled water. The carcinogenic potential of KBrO3 was tested by administering doses of 500 or 250 ppm to rats for 110 weeks. Significantly elevated incidences of renal cell tumors in males and females and mesotheliomas of the peritoneum in males as compared to controls were observed. When female mice were given KBrO3 at doses of 1000 or 500 ppm for 78 weeks, no significant differences in tumor incidences between experimental and control groups were apparent. NaClO was administered to male and female rats, respectively, at doses of 1000 or 500 ppm and 2000 or 1000 ppm for 104 weeks. In mice, NaClO was given at doses of 1000 or 500 ppm to either sex for 103 weeks. The incidences of tumors in NaClO-treated and control animals of both sexes were not significantly different in both rat and mouse studies. NaClO2 was given to rats of both sexes at a dose of 600 or 300 ppm for 85 weeks. No statistically significant differences were observed in the incidences of tumor formation between NaClO2-treated and control groups of both sexes. NaClO2 was administered to mice at a concentration of 500 or 250 ppm for 85 weeks. In males, the combined incidences of hyperplastic nodules and hepatocellular carcinomas of the liver in a low-dose group, and adenomas and adenocarcinomas of the lung in a high-dose group, were marginally increased compared to controls (p less than 0.05). However, these incidences in treated males were within the range of values of historical control data in our program. We concluded that KBrO3 was carcinogenic in rats of both sexes. NaClO was not carcinogenic in either rats and or mice under the conditions of the present studies. Although NaClO2 was shown to be noncarcinogenic in rats, the results for mice were evaluated as inconclusive. Also the results of two-stage mouse skin carcinogenesis using KBrO3, NaClO, and NaClO2 are presented. The necessity for further testing of oxidant chemicals to determine potential carcinogenic and/or promoting effects is suggested in view of the recently proposed role of active oxygen species in carcinogenesis.

Full text with graphs, charts and 35 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1474329/

Princess Takamatsu Symposium • January 1985

Risk evaluation of tumor-inducing substances in foods

Hayashi Y, Kurokawa Y, Maekawa A.

Abstract

“Carcinogenic risk assessment of chemicals consists of four phases, namely,

1) hazard identification,
2) exposure assessment,
3) hazard assessment or dose-response assessment, and
4) risk characterization.

The third phase of risk assessment is the evaluation of both hazard and exposure information to estimate the mathematical probability that the carcinogenic potential associated with an agent will be realized in the human population under defined conditions of exposure. The estimation of virtually safe dose (VSD) is regarded as a component of the third phase. Carcinogenic risk assessment is still at an embryonal stage of development, and there remains a number of problems to be clarified. With regard to the estimation of VSD, it is an important task to establish the principle for selection of appropriate mathematical models. The intention of this paper is to illustrate the estimation of VSD of two tumor-inducing chemicals, N-ethyl-N-nitrosourea and potassium bromate based on the dose-response data in animals and to discuss the biological implication of the estimated VSD in relation to the risk assessment of the chemicals in humans.”

http://www.ncbi.nlm.nih.gov/pubmed/3916202

“Eleven [food] additives; **calcium hypochlorite, cinnamic aldehyde, L-cysteine monohydrochloride, Food Green No. 3 (Fast Green FCF), hydrogen peroxide, potassium bromate, sodium chlorite, sodium hypochlorite, sodium nitrite, cacao pigment and caramel**, were positive in both the Ames test and the chromosome test.”

Food & Chemical Toxicology • August 1984

Primary mutagenicity screening of food additives currently used in Japan

Ishidate M Jr, Sofuni T, Yoshikawa K, Hayashi M,
Nohmi T, Sawada M, Matsuoka A.

Abstract

Salmonella/microsome tests (Ames tests) and chromosomal aberration tests in vitro using a Chinese hamster fibroblast cell line were carried out on 190 synthetic food additives and 52 food additives derived from natural sources, all of which are currently used in Japan. Fourteen out of 200 tested in the Ames assay showed positive effects and 54 out of 242 were positive in the chromosome test. Three additives (erythorbic acid, chlorine dioxide and beet red) were positive only in the Ames test, although their mutagenic potentials were relatively weak, while 43 additives were positive only in the chromosome test. Eleven additives (calcium hypochlorite, cinnamic aldehyde, L-cysteine monohydrochloride, Food Green No. 3 (Fast Green FCF), hydrogen peroxide, potassium bromate, sodium chlorite, sodium hypochlorite, sodium nitrite, cacao pigment and caramel) were positive in both the Ames test and the chromosome test. The usefulness of such primary screening tests combining two different genetic end-points, gene mutation and chromosomal aberration, and some correlation between mutagenicity and carcinogenicity of food additives are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/6381265

American Journal Of Nephrology • December 1984

Acute bromate poisoning associated with renal failure and deafness presenting as hemolytic uremic syndrome

Gradus D, Rhoads M, Bergstrom LB, Jordan SC.

Abstract

“A case of bromate-induced acute renal failure (ARF) in an infant associated with hemolysis, thrombocytopenia and deafness is presented. The initial clinical and laboratory features suggested the diagnosis of hemolytic uremic syndrome (HUS). The serum bromide level was in the nontoxic range (1.2 mg/dl). However, further investigation of the ingested material revealed the toxic agent to be bromate rather than bromide. The spectrum of bromate (BrO3-) toxicity is different from bromide (Br-) and includes the induction of ARF and deafness. **This combined with clinical evidence of behavioral regression and speech loss led to detection of deafness in this patient and confirmed the diagnosis of bromate toxicity.**”

http://www.ncbi.nlm.nih.gov/pubmed/6742011

“High incidences of renal cell tumors (in males and females given 500 or 250 ppm) and mesotheliomas of the peritoneum (in males given 500 ppm) were observed.”

Journal Of The National Cancer Institute • November 1983

Carcinogenicity of potassium bromate administered orally to F344 rats

Kurokawa Y, Hayashi Y, Maekawa A,
Takahashi M, Kokubo T, Odashima S.

Abstract

The carcinogenicity of potassium bromate, a food additive and a neutralizer in permanent waving, was tested by adding it to the drinking water of F344 rats for 110 weeks. Groups of 53 males and 53 females, each, were given solutions of 500 or 250 ppm of potassium bromate or distilled water. A concentration of 500 ppm markedly inhibited an increase of body weight of male rats. The mean survival time was shortest for males given 500 ppm (88.1 +/- 18.1 wk); the survival times of other groups were 101-104 weeks. The percentage survival in week 104 was relatively high in all groups, and it was 77.4% for males and 66.0% for females in the control group. High incidences of renal cell tumors (in males and females given 500 or 250 ppm) and mesotheliomas of the peritoneum (in males given 500 ppm) were observed. The incidences of these tumors in test groups were significantly higher than those in controls (P less than .001). It was concluded that, when orally administered under the conditions of this experiment, potassium bromate was carcinogenic to F344 rats.

http://www.ncbi.nlm.nih.gov/pubmed/6580498

CHAPTER NINE

Artificial Food Colors

The Peer Review

FD&C Yellow #5 • Tartrazine

FD&C Yellow #6

FD&C Blue #1

FD&C Blue #2

FD&C Green #3

FD&C Red #3

FD&C Red #40 and its Aluminum Lake

FD&C Lake Colors

Caramel Coloring & 4-Methylimidazole

And More

During the past 50 years the amount of synthetic dye used in foods has increased by 500%. Simultaneously, an alarming rise has occurred in behavioral problems in children, such as aggression, attention deficit disorder (ADD), and attention-deficit/hyperactivity disorder (ADHD). The ingestion of food delivers the greatest foreign antigenic load that challenges the immune system. Artificial colors can also be absorbed via the skin through cosmetic and pharmaceutical products. The molecules of synthetic colorants are small, and the immune system finds it difficult to defend the body against them. They can also bond to food or body proteins and, thus, are able to act in stealth mode to circumvent and disrupt the immune system. The consumption of synthetic food colors, and their ability to bind with body proteins, can have significant immunological consequences. This consumption can activate the inflammatory cascade, can result in the induction of intestinal permeability to large antigenic molecules, and could lead to cross-reactivities, autoimmunities, and even neurobehavioral disorders. The Centers for Disease Control (CDC) recently found a 41% increase in diagnoses of ADHD in boys of high-school age during the past decade. More shocking is the legal amount of artificial colorants allowed by the FDA in the foods, drugs, and cosmetics that we consume and use every day. ***The consuming public is largely unaware of the perilous truth behind the deceptive allure of artificial color.***

SOURCE: Alternative Therapies In Health And Medicine • February 2015: http://www.ncbi.nlm.nih.gov/pubmed/25599186

Colors
The Mainstream Perspective

BLUE 1
Beverages, candy, baked goods

One (unpublished) animal test suggested a small cancer risk, and a test-tube study indicated the dye might affect neurons. It also causes occasional allergic reactions. Blue 1 might be safe for people who are not allergic, but it should be better tested.

BLUE 2
Pet food, beverages, candy

Animal studies found some—but not conclusive—evidence that Blue 2 causes brain cancer in male rats, but the Food and Drug Administration concluded that there is "reasonable certainty" of no harm.

CITRUS RED 2
Skin of some Florida oranges only

The amounts of this rarely used dye that one might consume, even from eating marmalade, are so small that the risk is not worth worrying about.

GREEN 3
Candy, beverages

A 1981 industry-sponsored study gave hints of bladder and testes tumors in male rats, but FDA re-analyzed the data using other statistical tests and concluded that the dye was safe. Fortunately, this possibly carcinogenic dye is not widely used.

ORANGE B
Sausage

Approved for use only in sausage casings, high doses of this dye are harmful to the liver and bile duct. However, that is not worrisome because Orange B has not been used for many years.

RED 3
Candy, baked goods

The evidence that this dye caused thyroid tumors in rats is "convincing," according to a 1983 review committee report requested by FDA. FDA's recommendation that the dye be banned was overruled by pressure from the cherry industry and the U.S. Department of Agriculture. Red 3 used to color maraschino cherries, but it has been replaced there by the less controversial Red 40 dye. It is still used in a smattering of foods ranging from cake icing to fruit roll-ups to chewing gum.

RED 40
Soda pop, candy, gelatin desserts, pastries, pet food, sausage

The most widely used food dye. While this is one of the most-tested food dyes, the key mouse tests were flawed and inconclusive. An FDA review committee acknowledged problems, but said evidence of harm was not "consistent" or "substantial." Red 40 can cause allergy-like reactions. Like other dyes, Red 40 is used mainly in junk foods.

YELLOW 5
Gelatin dessert, candy, pet food, baked goods.

The second-most-widely used coloring causes allergy-like hypersensitivity reactions, primarily in aspirin-sensitive persons, and triggers hyperactivity in some children. It may be contaminated with such cancer-causing substances as benzidine and 4-aminobiphenyl (or chemicals that the body converts to those substances).

YELLOW 6
Beverages, candy, baked goods

Industry-sponsored animal tests indicated that this dye, the third-most-widely-used, causes tumors of the adrenal gland and kidney. In addition, small amounts of several carcinogens, such as 4-aminobiphenyl and benzidine (or chemicals that the body converts to those substances), contaminate Yellow 6. Yellow 6 does propose a significant health risk to humans. Yellow 6 may cause occasional, but sometimes-severe, hypersensitivity reactions. Let's look at the peer review and see what we find ...

WHAT IS TARTRAZINE?

Tartrazine is an azo dye, also known as FD&C Yellow No. 5 and is commonly used as a pharmaceutical colorant. It has been FDA-approved as a drug colorant for internal consumption, external use and around the eye area. In addition to use in pharmaceuticals as a dye, tartrazine is used as a food and cosmetic colorant. FD&C colors are the colors certified for use by the U.S. FDA, in the drug, food and cosmetic industry.

Over-the-counter and prescription drugs that contain tartrazine shall bear statements on the label stating that the product contains FD&C Yellow No. 5 (tartrazine) as a color additive or contains color additives including FD&C Yellow No. 5 (tartrazine). They may also state that FD&C Yellow No. 5 (tartrazine) may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. This warning statement shall appear in the "Precautions" section of the labeling.

Tartrazine hypersensitivity reactions include headaches, asthma attacks, itching or hives, insomnia, and hyperactivity. Tartrazine is often associated with allergies and hypersensitivity reactions, particularly in patients with asthma or aspirin intolerance. Tartrazine hypersensitivity reactions include headaches, asthma attacks, itching or hives, insomnia, and hyperactivity. The avoidance of tartrazine to prevent allergic asthma in these patients is controversial. A Cochrane Review from 2006 suggests that exclusion of tartrazine from the diets of patients with asthma does not worsen or improve asthma symptoms.

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http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=3cebab99372b0496f3e6d22cefed18da&rgn=div8&view=text&node=21:1.0.1.1.27.2.31.30&idno=21

“These findings indicated that prenatal exposure to ‘no observable adverse effect levels’ of Artificial food colourings and additives resulted in implicit adverse effects that caused an increase in motility and a decrease in motivation and anxiety in offspring in sex-related manner.”

Nutritional Neuroscience • January 2015

Are there any remarkable effects of prenatal exposure to food colourings on neurobehaviour and learning process in rat offspring?

Doguc DK, Aylak F, Ilhan I, Kulac E, Gultekin F.

Abstract

OBJECTIVE

Artificial food colourings and additives (AFCAs) have long been discussed to have adverse effects on cognition and behaviour in children. In this study, our aim was to assess the probable side effects of prenatal exposure to colouring food additives on neurobehaviour and spatial learning process.

METHODS

We administered ‘no observable adverse effect levels’ (NOAELs) of common used AFCAs as a mixture (erythrosine, Ponceau 4R, Allura Red AC, Sunset yellow FCF, tartrazine, Amaranth, Brilliant Blue, Azorubine and Indigotine) to female rats before and during gestation and tested their effects on spatial working memory and behaviour in their offspring. Effects of AFCAs on spatial working memory were evaluated by Morris water maze, behavioural and locomotor effects by open-field and forced-swim tests.

RESULTS

Prenatal exposure to commonly used AFCAs had no adverse effects on spatial working memory; however, assessment of interaction of sex and AFCAs on ‘latency to locate the visible platform’, which was used as a measure of motivation, showed a significant interaction ($P < 0.05$) on female rats. In addition, AFCAs caused an increase in anxiolytic like effect in the open-field test ($P < 0.05$) and an increase in mobility time ($P < 0.05$) in the forced-swim test. We also detected a significant interaction of sex and AFCAs on forced-swim test parameters ($P < 0.05$).

DISCUSSION

These findings indicated that prenatal exposure to NOAELs of AFCAs resulted in implicit adverse effects that caused an increase in motility and a decrease in motivation and anxiety in offspring in sex-related manner.

http://www.ncbi.nlm.nih.gov/pubmed/24257113

Pepto Bismol INGREDIENTS

Chewable Tablets

Each peppermint-flavoured chewable tablet contains bismuth subsalicylate 262 mg. Nonmedicinal ingredients: calcium carbonate, magnesium stearate, **mannitol, peppermint flavour, PVP, Red 27 Lake, sodium saccharin**, and **talc**.

Caplets

Each caplet contains bismuth subsalicylate 262 mg. Nonmedicinal ingredients: calcium carbonate, **magnesium stearate**, **mannitol, microcrystalline cellulose, polysorbate 80, PVP, Red 27 Lake, silica, and sodium carboxymethyl starch**.

Liquid Original

Each mL contains bismuth subsalicylate 17.6 mg. Nonmedicinal ingredients: **benzoic acid, D&C Red No. 22, D&C Red No. 28, flavour, magnesium aluminum silicate, methylcellulose, sodium saccharin, salicylic acid, sodium salicylate**, sorbic acid, and water.

Cherry-Flavoured

Each mL contains bismuth subsalicylate 17.6 mg. Nonmedicinal ingredients: **benzoic acid, D&C Red No. 22, D&C Red No. 28, flavour, magnesium aluminum silicate, methylcellulose, sodium saccharin, salicylic acid, sodium salicylate,** sorbic acid, **sucralose**, and water.

Liquid Extra Strength Original

Each mL contains bismuth subsalicylate 35.2 milligrams. Nonmedicinal ingredients: **benzoic acid, D&C Red No. 22, D&C Red No. 28, flavour, magnesium aluminum silicate, methylcellulose, sodium saccharin, salicylic acid, sodium salicylate**, sorbic acid, and water. *All ingredients in **bold** are either questionable or harmful food ingredients according to numerous peer reviewed reports and studies, including US government studies.

“The result indicates that consumption of food color in diet induces liver tissue damage.”

Toxicology International • January 2015

Food Color Induced Hepatotoxicity in Swiss Albino Rats, Rattus norvegicus

Author information

Saxena B1, Sharma S1.

Abstract

OBJECTIVE

Certain dietary constituents can induce toxicity and play a critical role in the development of several hepatic disorders. Tartrazine, metanil yellow and sunset yellow are widely used azo dyes in food products, so the present study is aimed to investigate the food color induced hepatotoxicity in Swiss albino rats.

MATERIALS AND METHODS

Swiss albino rats were divided into four groups, each group having six animals. Group I served as control, Group II, Group III and Group IV were administered with 25, 50 and 75 mg/kg body weight blend of sunset yellow, metanil yellow and tartrazine for 30 days. Hepatotoxicity in rats treated with a blend of these food colors was studied by assessing parameters such as serum total protein, serum albumin, serum alkaline phosphatase (ALP) as well as hepatic malondialdehyde (MDA). The activity of superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT) were assessed.

RESULTS

Significantly increased concentrations of serum total protein, serum albumin, serum ALP and hepatic MDA and significantly lowered levels of SOD, reduced GSH and CAT in the liver tissue of treated animals were observed when compared with control animals. The alteration in the liver includes necrosis of hepatocytes, infiltration and vacuolation.

CONCLUSION

The result indicates that consumption of food color in diet induces liver tissue damage. The used doses of food color were mostly attributable to hepatocellular damage and drastic alteration in antioxidant defense system.

Full text, graphs, charts and 24 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4721164/

“The results show that the Sunset Yellow and Brilliant Blue can have cytotoxic and genotoxic potential.”

Pakistan Journal Of Pharmaceutical Sciences • January 2015

Genotoxic and cytotoxic effects of Sunset Yellow and Brilliant Blue, colorant food additives, on human blood lymphocytes

Author information
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1. Bozok University, Science Institute, Department of Biology, Yozgat, Turkey
2. Bozok University, Faculty of Science and Art, Department of Biology, Yozgat, Turkey

Abstract

The synthetic dyes over fifty are used in many areas including the food industry around the world. Sunset Yellow FCF and Brilliant Blue FCF are used as colorant food additives in many food products. The present study investigated the genotoxic and cytotoxic effects of Sunset Yellow and Brilliant Blue. Genotoxic and cytotoxic activities of the food additives were evaluated in lymphocyte cell cultures using mitotic index, replication index and micronucleus assay. Mitotic index frequencies and replication index values were decreased and micronucleus frequency was increased with increasing concentrations of Sunset Yellow and Brilliant Blue. The changes in mitotic index and micronucleus are statistically significant ($p<0.05$). The results show that the Sunset Yellow and Brilliant Blue can have cytotoxic and genotoxic potential. It care must be taken when using these materials as a food additive.

http://www.ncbi.nlm.nih.gov/pubmed/25553699

“Azo dye has induced several chromosomal aberrations (genotoxic effect) at various stages of cell cycle such as stickiness of chromosomes, micronuclei formation, precocious migration of chromosome, unorientation, forward movement of chromosome, laggards, and chromatin bridge. Among all, stickiness of chromosomes was present in the highest frequency followed by partial genome elimination as micronuclei. **The present study suggests that extensive use of synthetic dyes should be forbidden due to genotoxic and cytotoxic impacts on living cells.**”

Journal Of Environmental And Public Health • January 2015

Genetic damage induced by a food coloring dye (sunset yellow) on meristematic cells of Brassica campestris L.

Author information

Dwivedi K1, Kumar G1.

Plant Genetics Laboratory, Department of Botany, University of Allahabad, Allahabad 211002, India

Abstract

We have performed the present piece of work to evaluate the effect of synthetic food coloring azo dye (sunset yellow) on actively dividing root tip cells of Brassica campestris L. Three doses of azo dye were administered for the treatment of actively dividing root tip cells, namely, 1%, 3%, and 5%, for 6-hour duration along with control. Mitotic analysis clearly revealed the azo dye induced endpoint deviation like reduction in the frequency of normal divisions in a dose dependent manner. Mitotic divisions in the control sets were found to be perfectly normal while dose based reduction in MI was registered in the treated sets. Azo dye has induced several chromosomal aberrations (genotoxic effect) at various stages of cell cycle such as stickiness of chromosomes, micronuclei formation, precocious migration of chromosome, unorientation, forward movement of chromosome, laggards, and chromatin bridge. Among all, stickiness of chromosomes was present in the highest frequency followed by partial genome elimination as micronuclei. The present study suggests that extensive use of synthetic dye should be forbidden due to genotoxic and cytotoxic impacts on living cells. Thus, there is an urgent need to assess potential hazardous effects of these dyes on other test systems like human and nonhuman biota for better scrutiny.

Full text, graphs, charts and 47 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4411456/

Alternative Therapies In Health And Medicine • February 2015

Immune reactivity to food coloring

By A. Vojdani and C. Vojdani

Abstract

Artificial food dyes are made from petroleum and have been approved by the US Food and Drug Administration (FDA) for the enhancement of the color of processed foods. They are widely used in the food and pharmaceutical industries to increase the appeal and acceptability of their products. Synthetic food colorants can achieve hues not possible for natural colorants and are cheaper, more easily available, and last longer. However, since the use of artificial food coloring has become widespread, many allergic and other immune reactive disorders have increasingly been reported.

During the past 50 y[ears], the amount of synthetic dye used in foods has increased by 500%. Simultaneously, an alarming rise has occurred in behavioral problems in children, such as aggression, attention deficit disorder (ADD), and attention-deficit/hyperactivity disorder (ADHD). The ingestion of food delivers the greatest foreign antigenic load that challenges the immune system. Artificial colors can also be absorbed via the skin through cosmetic and pharmaceutical products. The molecules of synthetic colorants are small, and the immune system finds it difficult to defend the body against them. They can also bond to food or body proteins and, thus, are able to act in stealth mode to circumvent and disrupt the immune system. The consumption of synthetic food colors, and their ability to bind with body proteins, can have significant immunological consequences. This consumption can activate the inflammatory cascade, can result in the induction of intestinal permeability to large antigenic molecules, and could lead to cross-reactivities, autoimmunities, and even neurobehavioral disorders. The Centers for Disease Control (CDC) recently found a 41% increase in diagnoses of ADHD in boys of high-school age during the past decade. More shocking is the legal amount of artificial colorants allowed by the FDA in the foods, drugs, and cosmetics that we consume and use every day. **The consuming public is largely unaware of the perilous truth behind the deceptive allure of artificial color.**

http://www.ncbi.nlm.nih.gov/pubmed/25599186

“Caramel color is added to many widely-consumed beverages as a colorant. **Consumers of these beverages can be exposed to 4-methylimidazole (4-MEI), a potential carcinogen** formed during its manufacture.”

PLoS One • February 2015

Caramel color in soft drinks and exposure to 4-methylimidazole: a quantitative risk assessment

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Abstract

Caramel color is added to many widely-consumed beverages as a colorant. Consumers of these beverages can be exposed to 4-methylimidazole (4-MEI), a potential carcinogen formed during its manufacture. California’s Proposition 65 law requires that beverages containing 4-MEI concentrations corresponding to exposures that pose excess cancer risks > 1 case per 100,000 exposed persons (29 µg 4-MEI/day) carry warning labels. Using ultrahigh-performance liquid chromatography-tandem mass spectrometry, we assessed 4-MEI concentrations in 12 beverages purchased in California and a geographically distant metropolitan area (New York) in which warning labels are not required. In addition, we characterized beverage consumption by age and race/ethnicity (using weighted means calculated from logistic regressions) and assessed 4-MEI exposure and resulting cancer risks and US population cancer burdens attributable to beverage consumption. Data on beverage consumption were obtained from the National Health and Nutrition Examination Survey, dose-response data for 4-MEI were obtained from the California Environmental Protection Agency Office of Environmental Health Hazards Assessment, and data on population characteristics were obtained from the U.S. Census Bureau. Of the 12 beverages, Malta Goya had the highest 4-MEI concentration (915.8 to 963.3µg/L), lifetime average daily dose (LADD - 8.04x10-3 mg/kgBW-day), lifetime excess cancer risk (1.93x10-4) and burden (5,011 cancer cases in the U.S. population over 70 years); Coca-Cola had the lowest value of each (4-MEI: 9.5 to 11.7µg/L; LADD: 1.01x10-4 mg/kgBW-day; risk: 1.92x10-6; and burden: 76 cases). 4-MEI concentrations varied considerably by soda and state/area of purchase, but were generally consistent across lots of the same beverage purchased in the same state/area. Routine consumption of certain beverages can result in 4-MEI exposures > 29 µg/day. State regulatory standards appear to have been effective in reducing exposure to carcinogens in some beverages. Federal regulation of 4-MEI in caramel color may be appropriate.

Full text, graphs, charts and 26 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4333292/

4-METHYLIMIDAZOLE OR 4-MEL

4-MeI is formally derived from imidazole through replacement of the hydrogen in position 4 by a methyl group. It is a slightly yellowish solid. 4-MeI may be formed in the browning of certain foods through the Maillard reaction between carbohydrates and amino-containing compounds. In particular, it is found in roasted foods, grilled meats, coffee and in types of caramel coloring produced with ammonia-based processes. It may arise also by fermentation.

Concern has arisen about the presence of 4-MeI in caramel color (which is the single most widely used food and beverage coloring), typically at a concentration between 50 and 700 ppm. Dark beers and common brands of cola drinks may contain more than 100 µg of this compound per 12-ounce serving.

A 2007 study by the National Toxicology Program (NTP) examined the potential carcinogenicity of 4-MeI in mice and rats. When mice were fed average daily doses of 40, 80, or 170 mg of 4-MeI per kilogram of body weight for two years, increased rates of benign lung tumors (alveolar/bronchiolar adenomas) were seen in females at all examined doses; malignant lung tumors (alveolar/bronchiolar carcinomas) were seen in males administered the highest dose; and an increased combined rate of benign and malignant tumors was seen in males at the top dose and in females at the top two doses.

In January 2011, California added 4-MeI to its list of probable carcinogens and stipulated 29 µg per day as the "No Significant Risk Level" intake. Drinks with caramel coloring exceeding the California limits require warning labels. Studies have found levels of up to 700 µg per liter in cola soft drinks, up to 2000 µg per liter in coffee, and up to 28,000 µg/liter in dark beer.

The non-profit Center for Science in the Public Interest has petitioned the FDA to require the removal of methylimidazole-containing caramel colors from soft drinks completely.

In March 2012, both Coca-Cola and Pepsi announced they had their caramel color suppliers modify their manufacturing processes to meet the new California standard; as of the announcement, the changes had already been made for beverages sold in California. The recipe is not changing in Europe, so the 4-MeI level will remain the same. Similarly, Pepsi and some Coke lots sold in the states other than California in the United States contain 4-MeI levels considered safe by the FDA and EFSA, but exceeding California standards—and they exceed moral, ethical and "Do No Harm" standards as well.

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“These data demonstrate that tartrazine may be harmful to health and its prolonged use could trigger carcinogenesis.”

Anticancer Research • March 2015

Effects on DNA repair in human lymphocytes exposed to the food dye tartrazine yellow

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Abstract

Tartrazine is a food additive that belongs to a class of artificial dyes and contains an azo group. Studies about its genotoxic, cytotoxic and mutagenic effects are controversial and, in some cases, unsatisfactory. This work evaluated the potential in vitro cytotoxicity, genotoxicity and effects on DNA repair of human lymphocytes exposed to the dye. We assessed the cytotoxicity of tartrazine by 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide test and the response of DNA repair through comet assay (alkaline version). We used different concentrations of the dye, ranging from 0.25-64.0 mM. The results demonstrated that tartrazine has no cytotoxic effects. However, this dye had a significant genotoxic effect at all concentrations tested. Although most of the damage was amenable to repair, some damage remained higher than positive control after 24 h of repair. These data demonstrate that tartrazine may be harmful to health and its prolonged use could trigger carcinogenesis.

http://www.ncbi.nlm.nih.gov/pubmed/25750299

“The amount certified has risen from 12 mg/capita/d in 1950 to 62 mg/capita/d in 2010 ... many children could be consuming far more dyes than previously thought.”

Clinical Pediatrics • April 2015

Amounts of artificial food dyes and added sugars in foods and sweets commonly consumed by children

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Abstract

Artificial food colors (AFCs) are used to color many beverages, foods, and sweets in the United States and throughout the world. In the United States, the Food and Drug Administration (FDA) limits the AFCs allowed in the diet to 9 different colors. The FDA certifies each batch of manufactured AFCs to guarantee purity and safety. The amount certified has risen from 12 mg/capita/d in 1950 to 62 mg/capita/d in 2010. Previously, we reported the amounts of AFCs in commonly consumed beverages. In this article, the amounts of AFCs in commonly consumed foods and sweets are reported. In addition, the amount of sugars in each product is included. Amounts of AFCs reported here along with the beverage data show that many children could be consuming far more dyes than previously thought. Clinical guidance is given to help caregivers avoid AFCs and reduce the amount of sugars in children’s diets.

http://www.ncbi.nlm.nih.gov/pubmed/24764054

“Our results show that the five artificial colorants studied bind better to HSA than their equivalent natural options, in terms of their H-bonding network, supporting the hypothesis of their potential risk to human health.”

Computational Biology And Chemistry • June 2015

Study on the interaction of artificial and natural food colorants with human serum albumin: A computational point of view

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Abstract

Due to the high amount of artificial food colorants present in infants’ diets, their adverse effects have been of major concern among the literature. Artificial food colorants have been suggested to affect children’s behavior, being hyperactivity the most common disorder. In this study we compare binding affinities of a group of artificial colorants (sunset yellow, quinoline yellow, carmoisine, allura red and tartrazine) and their natural industrial equivalents (carminic acid, curcumin, peonidin-3-glucoside, cyanidin-3-glucoside) to human serum albumin (HSA) by a docking approach and further refinement through atomistic molecular dynamics simulations. Due to the protein-ligand conformational interface complexity, we used collective variable driven molecular dynamics to refine docking predictions and to score them according to a hydrogen-bond criterion. With this protocol, we were able to rank ligand affinities to HSA and to compare between the studied natural and artificial food additives. Our results show that the five artificial colorants studied bind better to HSA than their equivalent natural options, in terms of their H-bonding network, supporting the hypothesis of their potential risk to human health.

http://www.ncbi.nlm.nih.gov/pubmed/25935119

“... a summary of evidence on possible detrimental effects of colorant mixes on children’s behaviour is provided and future research directions are outlined.”

Regulatory Toxicology And Pharmacology • December 2015

Health safety issues of synthetic food colorants

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Abstract

Increasing attention has been recently paid to the toxicity of additives used in food. The European Parliament and the Council published the REGULATION (EC) No. 1333/2008 on food additives establishing that the toxicity of food additives evaluated before 20th January 2009 must be re-evaluated by European Food Safety Authority (EFSA). The aim of this review is to survey current knowledge specifically on the toxicity issues of synthetic food colorants using official reports published by the EFSA and other available studies published since the respective report. Synthetic colorants described are Tartrazine, Quinoline Yellow, Sunset Yellow, Azorubine, Ponceau 4R, Erythrosine, Allura Red, Patent Blue, Indigo Carmine, Brilliant Blue FCF, Green S, Brilliant Black and Brown HT. Moreover, a summary of evidence on possible detrimental effects of colorant mixes on children’s behaviour is provided and future research directions are outlined.

http://www.ncbi.nlm.nih.gov/pubmed/26404013

“Results showed that both dyes induced significant cytotoxic and genotoxic effects in the cells, in concentrations much lower than those used in the commercial formula. Genotoxic effects could be related to the azo structure present in the composition of the dyes, which is known as mutagenic and carcinogenic.”

Food Chemistry Toxicology • December 2015

Cytotoxic and genotoxic effects of two hair dyes used in the formulation of black color

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Abstract

According to the International Agency for Research on Cancer (IARC), some hair dyes are considered mutagenic and carcinogenic in in vitro assays and exposed human populations. Epidemiological studies indicate that hairdressers occupationally exposed to hair dyes have a higher risk of developing bladder cancer. In Brazil, 26% of the adults use hair dye. In this study, we investigated the toxic effects of two hair dyes, Basic Red 51 (BR51) and Basic Brown 17 (BB17), which are temporary dyes of the azo group (R-N=N-R’), used in the composition of the black hair dye. To this end, MTT and trypan blue assays (cytotoxicity), comet and micronucleus assay (genotoxicity) were applied, with HepG2 cells. For cytotoxic assessment, dyes were tested in serial dilutions, being the highest concentrations those used in the commercial formula for hair dyes. For genotoxic assessment concentrations were selected according to cell viability. Results showed that both dyes induced significant cytotoxic and genotoxic effects in the cells, in concentrations much lower than those used in the commercial formula. Genotoxic effects could be related to the azo structure present in the composition of the dyes, which is known as mutagenic and carcinogenic. These results point to the hazard of the hair dye exposure to human health.

http://www.ncbi.nlm.nih.gov/pubmed/26404083

“The prolonged consumption of the blend [sunset yellow, metanil yellow and tartrazine] may cause adverse effect on human health.”

Toxicology International • January 2014

Serological changes induced by blend of sunset yellow, metanil yellow and tartrazine in swiss albino rat, rattus norvegicus

Author information

By B. Saxena and S. Sharma

Abstract

OBJECTIVE

The present study was carried out to evaluate the toxic effect of blend of some food colors on Swiss albino rats.

MATERIALS AND METHODS

A blend (1:1:1) of sunset yellow, metanil yellow and tartrazine showed additive effects on serological parameters which indicate that addition of these dye together in food stuff may give rise to more toxic effects than are produced by each dye individually. Animals were divided into four groups (I, II, III, and IV). First group was treated as control and respective group of animals received 25, 50 and 75 mg/kg body weight blend of food colors by gavaging up to 30 days.

RESULTS

The serological study showed a decrease in total protein and albumin and an increase in alkaline phosphatase, SGPT and total bilirubin. The results revealed that oral administration of these blend did not affect the body weight gain.

CONCLUSION

The prolonged consumption of the blend may cause adverse effect on human health.

Full text, graphs, charts and 22 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3989917/

“The amount of Artificial Food Colors the Food and Drug Administration has certified over the years has increased more than 5-fold since 1950 (12 mg/capita/day) to 2012 (68 mg/capita/day). In the past 38 years, there have been studies of adverse behavioral reactions such as hyperactivity in children to double-blind challenges with Artificial Food Colors.”

Clinical Pediatrics • February 2014

Amounts of artificial food colors in commonly consumed beverages and potential behavioral implications for consumption in children

Author information

Stevens LJ1, Burgess JR, Stochelski MA, Kuczek T., Purdue University, West Lafayette, IN, USA

Abstract

Artificial food colors (AFCs) are widely used to color foods and beverages. The amount of AFCs the Food and Drug Administration has certified over the years has increased more than 5-fold since 1950 (12 mg/capita/day) to 2012 (68 mg/capita/day). In the past 38 years, there have been studies of adverse behavioral reactions such as hyperactivity in children to double-blind challenges with AFCs. Studies that used 50 mg or more of AFCs as the challenge showed a greater negative effect on more children than those which used less. The study reported here is the first to quantify the amounts of AFCs in foods (specifically in beverages) commonly consumed by children in the United States. Consumption data for all foods would be helpful in the design of more challenge studies. The data summarized here should help clinicians advise parents about AFCs and beverage consumption.

http://www.ncbi.nlm.nih.gov/pubmed/24037921

“At 37°C the minimum concentration of Amaranth and Allura red at which significant DNA damage observed through comet assay was 1,250 µg/mL in 2nd hour post exposure time.”

Bulletin Of Environmental Contamination And Toxicology • January 2013

Genotoxicity assessment of amaranth and allura red using Saccharomyces cerevisiae

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Abstract

Amaranth (E123) and Allura red (E129), very important food azo dyes used in food, drug, paper, cosmetic and textile industries, were assessed for their genotoxic potential through comet assay in yeast cells. Comet assay was standardized by with different concentration of H(2)O(2). Concentrations of Amaranth and Allura red were maintained in sorbitol buffer starting from 9.76 to 5,000 µg/mL and 1 × 10(4) cells were incubated at two different incubation temperatures 28 and 37°C. Amaranth (E123) and Allura red (E129) were found to exhibit their genotoxic effect directly in Saccharomyces cerevisiae. No significant genotoxic activity was observed for Amaranth and Allura red at 28°C but at 37°C direct relation of Amaranth concentration with comet tail was significant and no positive relation was seen with time exposure factor. At 37°C the minimum concentration of Amaranth and Allura red at which significant DNA damage observed through comet assay was 1,250 µg/mL in 2nd h post exposure time. The results indicated that food colors should be carefully used in baking products as heavy concentration of food colors could affect the fermentation process of baking.

http://www.ncbi.nlm.nih.gov/pubmed/23132362

“All food colorants mixed with or without flavor additives induced a significant decrease in body weight, hemoglobin concentration and red blood cell count ... it is advisable to limit the uses of these food colorants and/or food flavor additives especially those used by children.”

Toxicology And Industrial Health • March 2013

Toxic effects of some synthetic food colorants and/or flavor additives on male rats

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Abstract

The objective of the present work was to evaluate the broadest toxic effect of some synthetic additives of colorants and/or flavors on different body organs and metabolic aspects in rats. A number of chemical food color and flavor additives are routinely added during processing to improve the aesthetic appearance of the dietary items. However, many of them are toxic after prolonged use. In this experiment, a total of 100 male albino rats of Spargue Dawley strain were divided into 10 groups: G(1) was fed basal diet and served as control, G(2): basal diet + Brilliant blue (blue dye, No. 2, 124 mg/kg diet), G(3): basal diet + carmoisine (red dye, No. 3, 70 mg/kg diet), G(4): basal diet + tartrazine (yellow dye, FD & C yellow No. 5, 75 mg/kg diet), G(5): basal diet + trans-anethole (4.5 g/kg diet) G(6): basal diet + propylene glycol (0.25 g/kg diet), G(7): basal diet + vanillin(1.25 g/kg diet), G(8): basal diet + Brilliant blue + propylene glycol, G(9): basal diet + carmoisine + trans-anethole, G(10): basal diet + tartrazine + vanillin for 42 successive days. All food colorants mixed with or without flavor additives induced a significant decrease in body weight, hemoglobin concentration and red blood cell count. Also there was a significant decrease in reduced glutathione content; glutathione-S-transferase and superoxide dismutase activities in both blood and liver compared to control group. On the other hand, a significant increase in serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase activities, bilirubin, urea, creatinine, total protein and albumin were observed in all test groups when compared to control group. Finally, it is advisable to limit the uses of these food colorants and/or food flavor additives especially those used by children.

http://www.ncbi.nlm.nih.gov/pubmed/22317828

“Studies have shown that a subgroup of children (with or without ADHD) react adversely to challenges with Artificial Food Colors. Many early studies found few children who reacted to challenges with 20-40 mg of AFCs. However, studies using at least 50 mg of AFCs showed a greater percentage of children who reacted to the challenge. Three types of potential mechanisms are explored: toxicological, antinutritional, and hypersensitivity.”

Nutritional Reviews • May 2013

Mechanisms of behavioral, atopic, and other reactions to artificial food colors in children

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Abstract

This review examines the research on mechanisms by which artificial food colors (AFCs) and common foods may cause behavioral changes in children with and without attention-deficit/hyperactivity disorder (ADHD). Children with ADHD show excess inattention, impulsivity, and hyperactivity. Studies have shown that a subgroup of children (with or without ADHD) react adversely to challenges with AFCs. Many early studies found few children who reacted to challenges with 20-40 mg of AFCs. However, studies using at least 50 mg of AFCs showed a greater percentage of children who reacted to the challenge. Three types of potential mechanisms are explored: toxicological, antinutritional, and hypersensitivity. Suggestions for future studies in animals and/or children include dose studies as well as studies to determine the effects of AFCs on the immune system, the intestinal mucosa, and nutrient absorption. Given the potential negative behavioral effects of AFCs, it is important to determine why some children may be more sensitive to AFCs than others and to identify the tolerable upper limits of exposure for children in general and for children at high risk.

http://www.ncbi.nlm.nih.gov/pubmed/23590704

“The monitoring of synthetic dyes in foods is very important due to their potential harmfulness to human beings.”

Food Chemistry • May 2012

Simultaneous determination of Sunset yellow and Tartrazine in soft drinks using gold nanoparticles carbon paste electrode

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Abstract

The monitoring of synthetic dyes in foods is very important due to their potential harmfulness to human beings. Herein, a carbon-paste electrode (CPE) that is chemically modified with gold nanoparticles (nAu) was fabricated and used for the determination of Sunset yellow (SY) and Tartrazine (Tz). Cyclic and differential pulse voltammetry (CV and DPV) results revealed two well-resolved anodic peaks for SY and Tz with remarkably increase in oxidation signals of these colourants. Based on this, a novel electrochemical method was developed for the simultaneous determination of SY and Tz. High sensitivity and selectivity, sub-micromolar detection limit, high reproducibility and regeneration of the electrode surface by simple polishing make the nAu-CPE electrode very suitable for the determination of SY and Tz in commercially available soft drinks. The detection limits was 3.0×10(-8) and 2.0×10(-9)moll(-1) for SY and Tz, respectively, which are remarkably lower than those reported previously for SY and Tz using other modified electrodes.

http://www.ncbi.nlm.nih.gov/pubmed/26434343

International Journal Of Occupational And Environmental Health • July 2012

Toxicology of food dyes

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Abstract

BACKGROUND
Food dyes, synthesized originally from coal tar and now petroleum, have long been controversial because of safety concerns. Many dyes have been banned because of their adverse effects on laboratory animals or inadequate testing.

CONCLUSIONS

> “This review finds that all of the nine currently US-approved dyes raise health concerns of varying degrees ... all of the currently used dyes should be removed from the food supply ...”

Red 3 causes cancer in animals, and there is evidence that several other dyes also are carcinogenic. Three dyes (Red 40, Yellow 5, and Yellow 6) have been found to be contaminated with benzidine or other carcinogens. At least four dyes (Blue 1, Red 40, Yellow 5, and Yellow 6) cause hypersensitivity reactions. Numerous microbiological and rodent studies of Yellow 5 were positive for genotoxicity. Toxicity tests on two dyes (Citrus Red 2 and Orange B) also suggest safety concerns, but Citrus Red 2 is used at low levels and only on some Florida oranges and Orange B has not been used for several years. The inadequacy of much of the testing and the evidence for carcinogenicity, genotoxicity, and hypersensitivity, coupled with the fact that dyes do not improve the safety or nutritional quality of foods, indicates that all of the currently used dyes should be removed from the food supply and replaced, if at all, by safer colorings. It is recommended that regulatory authorities require better and independent toxicity testing, exercise greater caution regarding continued approval of these dyes, and in the future approve only well-tested, safe dyes.

http://www.ncbi.nlm.nih.gov/pubmed/23026007

International Journal Of Occupational And Environmental Health • July 2012

Carcinogenicity and regulation of caramel colorings

Author information

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Abstract

“2- and 4-methylimidazoles are present as contaminants in caramel colorings manufactured with ammonia catalysts. Both contaminants have been shown to induce cancer in animals and may be present in caramel colorings in amounts that exceed federal guidelines. California requires warning notices on products that could lead to consumption of more than 30 micrograms per day. The US Food and Drug Administration should bar the use of excessively contaminated caramel coloring in food.”

http://www.ncbi.nlm.nih.gov/pubmed/23026009

“Artificial Food Colorings are not a major cause of ADHD per se, but seem to affect children regardless of whether or not they have ADHD, and they may have an aggregated effect on classroom climate if most children in the class suffer a small behavioral decrement with additive or synergistic effects.”

2- and 4-methylimidazoles

Testing on 110 samples of soda brands carried out by the Consumer Reports researchers, led by a team at the Johns Hopkins Center for a Livable Future in Baltimore, MD, found that drinks contained levels ranging from a low of 9.5 micrograms per liter (mcg/L) to an unbelievable high of 963 mcg/L. California requires a warning label for anything over 30 mcg/L. For people drinking several cans of any brown, caramel colored beverage every day, the future might not be promising. The report titled, “*Toxicity and carcinogenicity studies of 4-methylimidazole in F344/N rats and B6C3F1 mice*,” is a US government study. It finds a “*significant increase in the rates of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, alveolar epithelial hyperplasia and mononuclear cell leukemia*” related to ingestion of 2- and 4-methylimidazoles.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2366200/

Neurotherapeutics • July 2012

Artificial food colors and attention-deficit/hyperactivity symptoms: **conclusions to dye for**

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Abstract

The effect of artificial food colors (AFCs) on child behavior has been studied for more than 35 years, with accumulating evidence from imperfect studies. This article summarizes the history of this controversial topic and testimony to the 2011 Food and Drug Administration Food Advisory Committee convened to evaluate the current status of evidence regarding attention-deficit/hyperactivity disorder (ADHD). Features of ADHD relevant to understanding the AFC literature are explained: ADHD is a quantitative diagnosis, like hypertension, and some individuals near the threshold may be pushed over it by a small symptom increment. The chronicity and pervasiveness make caregiver ratings the most valid measure, albeit subjective. Flaws in many studies include non-standardized diagnosis, questionable sample selection, imperfect blinding, and non-standardized outcome measures. Recent data suggest a small but significant deleterious effect of AFCs on children’s behavior that is not confined to those with diagnosable ADHD. AFCs appear to be more of a public health problem than an ADHD problem. AFCs are not a major cause of ADHD per se, but seem to affect children regardless of whether or not they have ADHD, and they may have an aggregated effect on classroom climate if most children in the class suffer a small behavioral decrement with additive or synergistic effects. Possible biological mechanisms with published evidence include the effects on nutrient levels, genetic vulnerability, and changes in electroencephalographic beta-band power. A table clarifying the Food and Drug Administration and international naming systems for AFCs, with cross-referencing, is provided.

Full text, PDF, graphs, charts and 56 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3441937/pdf/13311_2012_Article_133.pdf

Annual Reviews Of Food Science And Technology • November 2011

Alternatives to those artificial FD&C food colorants

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Abstract

“Replacement of artificial food dyes with natural colorants is a current marketing trend, notwithstanding the fact that neither the United States nor the European Union (EU) has defined natural with respect to food colors. Consumer groups have concerns over the safety of synthetic colorants, and in addition, many of the naturally derived colorants provide health benefits. Food scientists frequently have the assignment of replacing artificial colorants with natural alternatives. This can be challenging, as naturally derived colorants are usually less stable, and all desired hues might, in fact, not be obtainable. In this review, the chemical and physical properties, limitations, and more suitable applications for those colorants that are legally available as substitutes for the synthetic colorants are summarized. Issues and challenges for certain foods are discussed, and in addition, colorants that may be available in the future are briefly described.”

http://www.ncbi.nlm.nih.gov/pubmed/22385164

“The decline in the activities of catalase, glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) as well as a rise in the level of malonaldehyde (MDA) were observed in the brain of tartrazine-treated rats, and these changes were associated with the brain from oxidative damage.”

Journal Of Food Science • August 2011

Effect of food azo dye tartrazine on learning and memory functions in mice and rats, and the possible mechanisms involved

Author information

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Abstract

Tartrazine is an artificial azo dye commonly used in human food and pharmaceutical products. The present study was conducted to evaluate the toxic effect of tartrazine on the learning and memory functions in mice and rats. Animals were administered different doses of tartrazine for a period of 30 d and were evaluated by open-field test, step-through test, and Morris water maze test, respectively. Furthermore, the biomarkers of the oxidative stress and pathohistology were also measured to explore the possible mechanisms involved. The results indicated that tartrazine extract significantly enhanced active behavioral response to the open field, increased the escape latency in Morris water maze test and decreased the retention latency in step-through tests. The decline in the activities of catalase, glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) as well as a rise in the level of malonaldehyde (MDA) were observed in the brain of tartrazine-treated rats, and these changes were associated with the brain from oxidative damage. The dose levels of tartrazine in the present study produced a few adverse effects in learning and memory functions in animals. The mechanisms might be attributed to promoting lipid peroxidation products and reactive oxygen species, inhibiting endogenous antioxidant defense enzymes and the brain tissue damage.

PRACTICAL APPLICATION

Tartrazine is an artificial azo dye commonly used in human food and pharmaceutical products. Since the last assessment carried out by the Joint FAO/WHO Expert Committee on Food Additives in 1964, many new studies have been conducted. However, there is a little information about the effects on learning and memory performance. The present study was conducted to evaluate the toxic effect of tartrazine on the learning and memory functions in animals and its possible mechanism involved. Based on our results, we believe that more extensive assessment of food additives in current use is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/22417523

“Replacement of artificial food dyes with natural colorants is a current marketing trend ... [but] neither the United States nor the European Union (EU) has defined natural with respect to food colors. Consumer groups have concerns over the safety of synthetic colorants, and in addition, many of the naturally derived colorants provide health benefits.”

Annual Review Of Food Science Technology • November 2012

Alternatives to those artificial FD&C food colorants

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Abstract

Replacement of artificial food dyes with natural colorants is a current marketing trend, notwithstanding the fact that neither the United States nor the European Union (EU) has defined natural with respect to food colors. Consumer groups have concerns over the safety of synthetic colorants, and in addition, many of the naturally derived colorants provide health benefits. Food scientists frequently have the assignment of replacing artificial colorants with natural alternatives. This can be challenging, as naturally derived colorants are usually less stable, and all desired hues might, in fact, not be obtainable. In this review, the chemical and physical properties, limitations, and more suitable applications for those colorants that are legally available as substitutes for the synthetic colorants are summarized. Issues and challenges for certain foods are discussed, and in addition, colorants that may be available in the future are briefly described.

http://www.ncbi.nlm.nih.gov/pubmed/22385164

“We concluded that tartrazine and carmoisine affect adversely and alter biochemical markers in vital organs e.g. liver and kidney not only at higher doses but also at low doses.”

Food And Chemical Toxicology • October 2010

Effect of food azo dyes tartrazine and carmoisine on biochemical parameters related to renal, hepatic function and oxidative stress biomarkers in young male rats

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Abstract

Tartrazine and carmoisine are an organic azo dyes widely used in food products, drugs and cosmetics. The present study conducted to evaluate the toxic effect of these coloring food additives; on renal, hepatic function, lipid profile, blood glucose, body-weight gain and biomarkers of oxidative stress in tissue. Tartrazine and carmoisine were administered orally in two doses, one low and the other high dose for 30 days followed by serum and tissue sample collection for determination of ALT, AST, ALP, urea, creatinine, total protein, albumin, lipid profile, fasting blood glucose in serum and estimation of GSH, catalase, SOD and MDA in liver tissue in male albino rat. Our data showed a significant increase in ALT, AST, ALP, urea, creatinine total protein and albumin in serum of rats dosed with tartrazine and carmoisine compared to control rats and these significant change were more apparent in high doses than low, GSH, SOD and Catalase were decreased and MDA increased in tissue homogenate in rats consumed high tartrazine and both doses of carmoisine. We concluded that tartrazine and carmoisine affect adversely and alter biochemical markers in vital organs e.g. liver and kidney not only at higher doses but also at low doses.

http://www.ncbi.nlm.nih.gov/pubmed/20678534

“Our results indicate that these food colorants had a toxic potential to human lymphocytes in vitro and it seems that they bind directly to DNA.”

Food And Chemical Toxicology • October 2010

Cytogenetic evaluation and DNA interaction studies of the food colorants amaranth, erythrosine and tartrazine

Author information

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Abstract

Food coloring agents, amaranth, erythrosine and tartrazine have been tested at 0.02-8mM in human peripheral blood cells in vitro, in order to investigate their genotoxic, cytotoxic and cytostatic potential. Amaranth at the highest concentration (8mM) demonstrates high genotoxicity, cytostaticity and cytotoxicity. The frequency of SCEs/cell was increased 1.7 times over the control level. Additionally, erythrosine at 8, 4 and 2mM shows a high cytotoxicity and cytostaticity. Finally, tartrazine seems to be toxic at 8 and 4mM. No signs of genotoxicity were observed. Reversely, tartrazine showed cytotoxicity at 1 and 2mM. Furthermore, spectroscopic titration studies for the interaction of these food additives with DNA showed that these dyes bind to calf thymus DNA and distinct isosbestic points are observed clearly suggesting binding of the dyes to DNA. Additionally DNA electrophoretic mobility experiments showed that these colorants are obviously capable for strong binding to linear dsDNA causing its degradation. PCR amplification of all DNA fragments (which previously were pre-treated with three different concentrations of the colorants, extracted from agarose gel after separation and then purified), seems to be attenuated with a manner dye concentration-dependent reflecting in a delayed electrophoretic mobility due to the possible binding of some molecules of the dyes. Evaluation of the data and curves were obtained after quantitative and qualitative analysis of the lanes of the gel by an analyzer computer program. Our results indicate that these food colorants had a toxic potential to human lymphocytes in vitro and it seems that they bind directly to DNA.

http://www.ncbi.nlm.nih.gov/pubmed/20667460

“This result suggests that superoxide anions, originating on dyes by light irradiation, must attack drug-metabolizing enzymes. It is possible that red cosmetics containing phloxine, erythrosine, or rose bengal react with proteins on skin under lighting and may lead to rough skin.”

Journal Of Environmental Public Health • August 2009

Toxicity of xanthene food dyes by inhibition of human drug-metabolizing enzymes in a noncompetitive manner

Author information

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Abstract

The synthetic food dyes studied were rose bengal (RB), phroxine (PL), amaranth, erythrosine B (ET), allura red, new coccine, acid red (AR), tartrazine, sunset yellow FCF, brilliant blue FCF, and indigo carmine. First, data confirmed that these dyes were not substrates for CYP2A6, UGT1A6, and UGT2B7. ET inhibited UGT1A6 (glucuronidation of p-nitrophenol) and UGT2B7 (glucuronidation of androsterone). We showed the inhibitory effect of xanthene dye on human UGT1A6 activity. Basic ET, PL, and RB in those food dyes strongly inhibited UGT1A6 activity, with IC(50) values = 0.05, 0.04, and 0.015 mM, respectively. Meanwhile, AR of an acidic xanthene food dye showed no inhibition. Next, we studied the inhibition of CYP3A4 of a major phase I drug-metabolizing enzyme and P-glycoprotein of a major transporter by synthetic food dyes. Human CYP3A4 and P-glycoprotein were also inhibited by basic xanthene food dyes. The IC(50) values of these dyes to inhibit CYP3A4 and P-glycoprotein were the same as the inhibition level of UGT1A6 by three halogenated xanthene food dyes (ET, PL, and RB) described above, except AR, like the results with UGT1A6 and UGT2B7. We also confirmed the noninhibition of CYP3A4 and P-gp by other synthetic food dyes. Part of this inhibition depended upon the reaction of (1)O(2) originating on xanthene dyes by light irradiation, because inhibition was prevented by (1)O(2) quenchers. We studied the influence of superoxide dismutase and catalase on this inhibition by dyes and we found prevention of inhibition by superoxide dismutase but not catalase. This result suggests that superoxide anions, originating on dyes by light irradiation, must attack drug-metabolizing enzymes. It is possible that red cosmetics containing phloxine, erythrosine, or rose bengal react with proteins on skin under lighting and may lead to rough skin.

Full text, graphs, charts and 52 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2778353/

“Data indicated that combinations of tar colors may adversely affect both developmental and adult hippocampal neurogenesis ...”

Journal Of Toxicology And Environmental Health - Part A • December 2009

Risk assessment for the combinational effects of food color additives: neural progenitor cells and hippocampal neurogenesis

Author information

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Abstract

In 2006, the Korea Food and Drug Administration reported that combinations of dietary colors such as allura red AC (R40), tartrazine (Y4), sunset yellow FCF (Y5), amaranth (R2), and brilliant blue FCF (B1) are widely used in food manufacturing. Although individual tar food colors are controlled based on acceptable daily intake (ADI), there is no apparent information available for how combinations of these additives affect food safety. In the current study, the potencies of single and combination use of R40, Y4, Y5, R2, and B1 were examined on neural progenitor cell (NPC) toxicity, a biomarker for developmental stage, and neurogenesis, indicative of adult central nervous system (CNS) functions. R40 and R2 reduced NPC proliferation and viability in mouse multipotent NPC, in the developing CNS model. Among several combinations tested in mouse model, combination of Y4 and B1 at 1000-fold higher than average daily intake in Korea significantly decreased numbers of newly generated cells in adult mouse hippocampus, indicating potent adverse actions on hippocampal neurogenesis. However, other combinations including R40 and R2 did not affect adult hippocampal neurogenesis in the dentate gyrus. Evidence indicates that single and combination use of most tar food colors may be safe with respect to risk using developmental NPC and adult hippocampal neurogenesis. However, the response to excessively high dose combination of Y4 and B1 is suggestive of synergistic effects to suppress proliferation of NPC in adult hippocampus. Data indicated that combinations of tar colors may adversely affect both developmental and adult hippocampal neurogenesis; thus, further extensive studies are required to assess the safety of these additive combinations.

http://www.ncbi.nlm.nih.gov/pubmed/20077213

“4MI is carcinogenic inducing alveolar/bronchiolar adenoma and carcinoma in male and female mice. 4MI may also induce mononuclear cell leukemia in female rats.”

Archives In Toxicology • January 2008

Toxicity and carcinogenicity studies of 4-methylimidazole in F344/N rats and B6C3F1 mice

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Abstract

4-Methylimidazole (4MI) is used in the manufacture of pharmaceuticals, photographic chemicals, dyes and pigments, cleaning and agricultural chemicals, and rubber. It has been identified as a by-product of fermentation in foods and has been detected in mainstream and side stream tobacco smoke. 4MI was studied because of its high potential for human exposure. Groups of 50 male and 50 female F344/N rats were fed diets containing 0-, 625-, 1,250-, or 2,500 ppm 4MI (males) or 0-, 1,250-, 2,500-, or 5,000 ppm 4MI (females) for 106 weeks. Based on the food consumption the calculated average daily doses were approximately 30, 55, or 115 mg 4MI/kg body weight to males and 60, 120, or 250 mg 4MI/kg to females. Survival of all exposed groups of males and females was similar to that of the control groups. The mean body weights of males in the 1,250- and 2,500 ppm groups and females in the 2,500- and 5,000 ppm groups were less than those of the control groups throughout the study. Feed consumption by 5,000 ppm females was less than that by the controls. Clonic seizures, excitability, hyperactivity, and impaired gait were observed primarily in 2,500- and 5,000 ppm females. The incidence of mononuclear cell leukemia in the 5,000 ppm females was significantly greater than that in the controls. The incidences of hepatic histiocytosis, chronic inflammation, and focal fatty change were significantly increased in all exposed groups of male and female rats. The incidences of hepatocellular eosinophilic and mixed cell foci were significantly increased in 2,500 ppm males and 5,000 ppm females. Groups of 50 male and 50 female B6C3F1 mice were fed diets containing 0-, 312-, 625-, or 1,250 ppm 4MI for 106 weeks. Based on the food consumption the calculated average daily doses were approximately 40, 80, or 170 mg 4MI/kg body weight to males and females. Survival of all exposed groups of males and females was similar to that of the control groups. Mean body weights of males and females in the 1,250 ppm groups and that in the 312- and 625 ppm females were less than those of the control groups. Feed consumption by exposed groups of male and female mice was similar to that by the controls. The incidences of alveolar/bronchiolar adenoma in all exposed groups of females, alveolar/bronchiolar carcinoma in 1,250 ppm males, and alveolar/bronchiolar adenoma or carcinoma (combined) in 1,250 ppm males and 625- and 1,250 ppm females were significantly greater than those in the control groups. The incidence of alveolar epithelial hyperplasia was significantly increased in the 1,250 ppm females. 4MI is carcinogenic inducing alveolar/bronchiolar adenoma and carcinoma in male and female mice. 4MI may also induce mononuclear cell leukemia in female rats.

Full text, graphs, charts and 37 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2366200/

Talanta • February 2008

Determination of 40 synthetic food colors in drinks and candies by high-performance liquid chromatography using a short column with photodiode array detection

Author information

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Abstract

Forty synthetic food colors were determined in drinks and candies by reversed-phase high-performance liquid chromatography with photodiode array detection. The following food colors were analyzed within 19 min using a short analytical column (50 mm x 4.6 mm i.d., 1.8 microm) at 50 degrees C with gradient elution: Ponceau 6R, Tartrazine, Fast yellow AB, Amaranth, Indigotine, Naphthol yellow S, Chrysoine, Ponceau 4R, Sunset yellow FCF, Red 10B, Orange G, Acid violet 7, Brilliant black PN, Allura red AC, Yellow 2G, Red 2G, Uranine, Fast red E, Green S, Ponceau 2R, Azorubine, Orange I, Quinoline yellow, Martius yellow, Ponceau SX, Ponceau 3R, Fast green FCF, Eosine, Brilliant blue FCF, Orange II, Orange RN, Acid blue 1, Erythrosine, Amido black 10B, Acid red 52, Patent blue V, Acid green 9, Phloxine B, Benzyl violet 4B, and Rose bengal. The recoveries of these compounds added to soft drinks and candies at 5 microg/g ranged from 76.6 to 115.0%, and relative standard deviations (R.S.D.s) were within 6.0%. The limits of detection and the limits of quantitation were 0.03 and 0.1 microg/g, respectively.

http://www.ncbi.nlm.nih.gov/pubmed/18371797

“... out of nine permitted colours, four exceeded their Acceptable Daily Intakes by factors of 2-8: tartrazine, sunset yellow, carmoisine and allura red.”

Food Additives And Contaminants • March 2006

Estimates of dietary exposure of children to artificial food colours in Kuwait

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Abstract

To assess the intake of artificial food colour additives by 5-14-year-old children in the State of Kuwait, a 24-h dietary recall was conducted twice on 3141 male and female Kuwaiti and non-Kuwaiti children from 58 schools. The determination of colour additives in 344 foods items consumed was performed using high-performance liquid chromatography with diode array detector. A comparison with the Food and Agriculture Organization and World Health Organization acceptable daily intakes (ADIs) was undertaken to evaluate the potential risk associated with the consumption of artificial colour additives by children in Kuwait. The results indicated that out of nine permitted colours, four exceeded their ADIs by factors of 2-8: tartrazine, sunset yellow, carmoisine and allura red. Further, follow-up studies to provide insight into potential adverse health effects associated with the high intakes of these artificial colour additives on the test population are warranted.

http://www.ncbi.nlm.nih.gov/pubmed/16517526

“Omission and inaccuracy of drug labeling information on pharmaceutical excipients may expose susceptible individuals to adverse reactions caused by preservatives and dyes.”

Brazilian Journal Of Otorhinolaryngology • May 2006

Pharmaceutical excipients and the information on drug labels

Author information

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Abstract

AIM

To evaluate the presence of preservatives, dyes, sweeteners and flavouring substances in 73 pharmaceutical preparations of 35 medicines for oral administration, according to drug labeling information about the excipients.

METHODS

35 medications were selected, both over-the-counter and prescription drugs, marketed in Brazil. The sample included: analgesic/antipyretic, antimicrobial, muco-regulatory, cough and cold, decongestant, antihistamine, bronchodilator, corticosteroid, antiinflammatory and vitamin medications. We collected data on 73 preparations of these drugs, according to drug labeling information regarding preservatives, dyes, sweeteners and flavourings.

RESULTS

Methylparaben and propylparaben were the most common preservatives found (43% and 35.6% respectively). The most common sweeteners were: sucrose (sugar) (53.4%), sodium saccharin (38.3%) and sorbitol (36.9%). Twenty-one medicines (28,7%) contained two sweeteners. Colourless medicines predominated (43.8%), followed by those with sunset yellow dye (FD&C yellow no. 6) (15%). Five products (6.8%) contained more than one colour agent. Tartrazine (FD&C yellow no. 5) was present in seven preparations (9.5%). Fruit was the most common flavouring found (83%). Labelings of drugs which contained sugar frequently omitted its exact concentration (77%). Of the four labelings of medicines which contained aspartame, two did not warn patients regarding phenylketonuria.

CONCLUSION

Omission and inaccuracy of drug labeling information on pharmaceutical excipients may expose susceptible individuals to adverse reactions caused by preservatives and dyes. Complications of inadvertent intake of sugar-containing medicines by diabetics, or aspartame intake by patients with phenylketonuria may also occur.

http://www.ncbi.nlm.nih.gov/pubmed/17119779

“Of all the additives, dyes were the most genotoxic. Amaranth, Allura Red, New Coccine, Tartrazine, Erythrosine, Phloxine, and Rose Bengal induced dose-related DNA damage in the glandular stomach, colon, and/or urinary bladder.

All seven dyes induced DNA damage in the gastrointestinal organs at a low dose (10 or 100mg/kg). Among them, Amaranth, Allura Red, New Coccine, and Tartrazine induced DNA damage in the colon at close to the acceptable daily intakes (ADIs).

Two antioxidants (butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)), three fungicides (biphenyl, sodium o-phenylphenol, and thiabendazole), and four sweeteners (sodium cyclamate, saccharin, sodium saccharin, and sucralose) also induced DNA damage in gastrointestinal organs.”

http://www.ncbi.nlm.nih.gov/pubmed/12160896

Mutation Research • August 2002

The comet assay with 8 mouse organs: results with 39 currently used food additives

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Abstract

We determined the genotoxicity of 39 chemicals currently in use as food additives. They fell into six categories-dyes, color fixatives and preservatives, preservatives, antioxidants, fungicides, and sweeteners. We tested groups of four male ddY mice once orally with each additive at up to 0.5xLD(50) or the limit dose (2000mg/kg) and performed the comet assay on the glandular stomach, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow 3 and 24h after treatment. Of all the additives, dyes were the most genotoxic. Amaranth, Allura Red, New Coccine, Tartrazine, Erythrosine, Phloxine, and Rose Bengal induced dose-related DNA damage in the glandular stomach, colon, and/or urinary bladder. All seven dyes induced DNA damage in the gastrointestinal organs at a low dose (10 or 100mg/kg). Among them, Amaranth, Allura Red, New Coccine, and Tartrazine induced DNA damage in the colon at close to the acceptable daily intakes (ADIs). Two antioxidants (butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)), three fungicides (biphenyl, sodium o-phenylphenol, and thiabendazole), and four sweeteners (sodium cyclamate, saccharin, sodium saccharin, and sucralose) also induced DNA damage in gastrointestinal organs. Based on these results, we believe that more extensive assessment of food additives in current use is warranted.

“We determined the genotoxicity of synthetic red tar dyes currently used as food color additives in many countries, including JAPAN ... Because the 3 azo additives we examined induced colon DNA damage at a very low dose, more extensive assessment of azo additives is warranted.”

Toxicology Science • May 2001

DNA damage induced by red food dyes orally administered to pregnant and male mice

Author information

Tsuda S1, Murakami M, Matsusaka N, Kano K, Taniguchi K, Sasaki YF.

Abstract

We determined the genotoxicity of synthetic red tar dyes currently used as food color additives in many countries, including JAPAN: For the preliminary assessment, we treated groups of 4 pregnant mice (gestational day 11) once orally at the limit dose (2000 mg/kg) of amaranth (food red No. 2), allura red (food red No. 40), or acid red (food red No. 106), and we sampled brain, lung, liver, kidney, glandular stomach, colon, urinary bladder, and embryo 3, 6, and 24 h after treatment. We used the comet (alkaline single cell gel electrophoresis) assay to measure DNA damage. The assay was positive in the colon 3 h after the administration of amaranth and allura red and weakly positive in the lung 6 h after the administration of amaranth. Acid red did not induce DNA damage in any sample at any sampling time. None of the dyes damaged DNA in other organs or the embryo. We then tested male mice with amaranth, allura red, and a related color additive, new coccine (food red No. 18). The 3 dyes induced DNA damage in the colon starting at 10 mg/kg. Twenty ml/kg of soaking liquid from commercial red ginger pickles, which contained 6.5 mg/10 ml of new coccine, induced DNA damage in colon, glandular stomach, and bladder. The potencies were compared to those of other rodent carcinogens. The rodent hepatocarcinogen p-dimethylaminoazobenzene induced colon DNA damage at 1 mg/kg, whereas it damaged liver DNA only at 500 mg/kg. Although 1 mg/kg of N-nitrosodimethylamine induced DNA damage in liver and bladder, it did not induce colon DNA damage. N-nitrosodiethylamine at 14 mg/kg did not induce DNA damage in any organs examined. Because the 3 azo additives we examined induced colon DNA damage at a very low dose, more extensive assessment of azo additives is warranted.

Full text, graphs, charts and 45 references

http://toxsci.oxfordjournals.org/content/61/1/92.long

“High psychiatric morbidity has been reported among those who complain of food intolerance or allergy. Many cases of food allergy or intolerance to drugs are not due to allergy to the food or drugs themselves, but to the additives used for coloring, flavoring, preserving, thickening, emulsifying, or stabilizing the product.”

Journal Of Clinical Psychiatry • July 2000

Allergy to tartrazine in psychotropic drugs

Author information

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Abstract

BACKGROUND

High psychiatric morbidity has been reported among those who complain of food intolerance or allergy. Many cases of food allergy or intolerance to drugs are not due to allergy to the food or drugs themselves, but to the additives used for coloring, flavoring, preserving, thickening, emulsifying, or stabilizing the product. Of various coloring dyes used, tartrazine (FD & C yellow no. 5) is the color most frequently incriminated in producing allergic reactions. The exact epidemiology and pattern of allergic reactions to tartrazine in psychotropic drugs have not been frequently studied and reported.

METHOD

The present study included consecutive outpatients (May 1996 to April 1998) who developed allergic reactions or intolerance to tartrazine in psychotropic drugs. Total patients exposed to tartrazine-containing drugs were also recorded. The subjects showing allergic reactions to tartrazine were then exposed to non-tartrazine-containing brands.

RESULTS

Of 2210 patients exposed to tartrazine-containing drugs, 83 (3.8%) developed allergic reactions. The symptoms subsided within 24 to 48 hours of stopping the drug. None of the patients showed allergy to non-tartrazine-containing brands. History of allergy to tartrazine was present in 13.2%, and 15.7% of patients had a history of aspirin sensitivity.

CONCLUSION

Tartrazine allergy should be considered in patients developing drug allergy, because it would require changing the brand rather than stopping treatment with that drug.

http://www.ncbi.nlm.nih.gov/pubmed/10937604

Food Additives And Contaminants • September 1999

Determination of benzidine in the food colours tartrazine and sunset yellow FCF, by reduction and derivatization followed by high-performance liquid chromatography

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Abstract

Free and bound benzidine, a non-sulphonated aromatic amine (NSAA), were determined in the food colours tartrazine and sunset yellow FCF. Bound amines were released by reducing with sodium dithionite, then total NSAAs were extracted into chloroform, transferred to aqueous acid solution and diazotized with sodium nitrite before coupling with 2-naphthol-3,6-disulphonic acid, disodium salt (R-salt). Coloured benzidine and aniline derivatives (BZDRS and ANRS) were analysed using reversed-phase ion pair high-performance liquid chromatography (HPLC) and an absorbance detector set at 548 nm. Levels of total benzidine were similar to those reported in studies conducted in the USA, and ranged from < 5 to 270 ng/g. Total aniline was also determined (0.2-188 micrograms/g). Recoveries of benzidine with this method were found to be lower than expected (average ca 46%), but were reproducible. Detection limits were 15-20 ng BZDRS/g (3-4 ng benzidine/g). Mass spectrometry (LC-MS) was evaluated for identifying and determining purity of the standards, but difficulties were encountered when the methodology was applied to commercial samples.

http://www.ncbi.nlm.nih.gov/pubmed/10755129

“The results showed clear immunosuppressive effects from the 2 substances tested ...” [Tartrazine & Amaranth]

Veterinary And Human Toxicology • February 1998

Immunological aspects of the common food colorants, amaranth and tartrazine

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Abstract

We describe a sensitive and reproducible microassay model using human peripheral blood lymphocytes (PBL) for discrimination between the cytotoxic and immunosuppressive effects of food colorants such as amaranth and tartrazine. The cytotoxic effects of a wide range of concentrations of these substances were studied on human PBL by the colorimetric in vitro cytotoxicity assays, neutral red uptake (NR) and thiazolyl blue tetrazolium bromide (MTT). The immunotoxic properties of these 2 substances were determined by a [3H]-thymidine DNA incorporation assay on phytohemagglutinin stimulated or non-stimulated lymphocytes, as well as by a Cr51 release Natural Killer assays. The results showed clear immunosuppressive effects from the 2 substances tested, although the concentrations chosen for this study proved to be non-cytotoxic by NR and MTT cytotoxic endpoints.

http://www.ncbi.nlm.nih.gov/pubmed/9467198

Allergy And Asthma Proceedings • January 1996

Occupational asthma caused by FD&C blue dye no. 2

Author information

Miller ME1, Lummus ZL, Bernstein DI.

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Abstract

"We report the case of a 55-year-old male who experienced cough, dyspnea, wheezing, and nasal congestion immediately upon exposure to FD&C Blue Dye No. 2 (Indigotine) at work. The patient had worked for 10 years mixing and grinding powdered synthetic red, yellow, and blue dyes for use in foods; symptoms had occurred for 2 years and only with exposure to Indigotine (C16H8N2Na2O8S2), a free flowing blue powder. Prick testing to Indigotine (20 mg/mL) was negative. ELISA failed to detect specific IgE, IgA, IgM, or IgG to Indigotine-HSA conjugates. Bronchial challenge was done according to the method of Pepys et al. beginning with 4 x 10(-4) lactose dilution of Indigotine powder. After 5 minutes of exposure to 4 gm Indigotine/100 gm lactose, the patient developed dyspnea and audible wheezing. At 20 minutes postexposure, there was a 20% decline in FEV1 from prechallenge baseline; no late phase response was observed. A second bronchial challenge with sodium sulfate, the major nondye product additive was negative. To our knowledge, this is the first documented case of occupational asthma due to FD&C Blue Dye No. 2. The pathogenesis is uncertain but does not appear to be IgE mediated."

http://www.ncbi.nlm.nih.gov/pubmed/8814938

Indian Journal Of Medical Sciences • August 1996

Allergy to tartrazine in alprazolam

Author information

By MS Bhatia

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College of Medical Sciences, Shahdara, Delhi

Abstract

“Allergy to tartrazine-containing psychotropic medication (especially antidepressants) had been reported. 20 patients of apparent allergy to tartrazine-containing alprazolam brands in 480 patients exposed to the dye are described. Rechallenge with non tartrazine-containing alprazolam brands did not produce the similar allergic reactions.”

http://www.ncbi.nlm.nih.gov/pubmed/9018987

“Sucrose was present in 63% (26/41) of preparations followed by lactose in 29% (12/41) of preparations. On average, a preparation contained two sweeteners. The FD&C yellow #6 (sunset yellow) was the most common dye, present in 46% (19/41) of the preparations followed by FD&C Red #40 in 29% (12/41). For 34% (14/41) of the preparations, no color or dye was identified by the manufacturers.”

Clinical Pediatrics • September 1996

Sweeteners, dyes, and other excipients in vitamin and mineral preparations

Author information

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Abstract

Multivitamins and mineral preparations are widely used for infants and children. All of these preparations contain a variety of excipients (“inert ingredients”). Excipients are generally safe; however, adverse effects have been attributed to them. Complete information about the excipients in various preparations is not readily available. The information about sweeteners, dyes, and other excipients (flavorings, preservatives, stabilizers, and fillers) for 41 chewable/liquid multivitamin and mineral preparations was obtained and tabulated. Sucrose was present in 63% (26/41) of preparations followed by lactose in 29% (12/41) of preparations. On average, a preparation contained two sweeteners. The FD&C yellow #6 (sunset yellow) was the most common dye, present in 46% (19/41) of the preparations followed by FD&C Red #40 in 29% (12/41). For 34% (14/41) of the preparations, no color or dye was identified by the manufacturers. The tables listing excipients and their adverse effects are presented and should be helpful to health care providers in selecting preparations containing individual excipients when an adverse reaction occurs or there exists a contraindication for using the excipient. The mandatory listing of all excipients is the only way to assure that physicians and consumers will be fully informed about the hidden ingredients.

http://www.ncbi.nlm.nih.gov/pubmed/8877241

“This study demonstrates a beneficial effect of eliminating reactive foods and artificial colors in children with ADHD. Dietary factors may play a significant role in the etiology of the majority of children with ADHD.”

Annals In Allergy • May 1994

Foods and additives are common causes of the attention deficit hyperactive disorder in children

Author information

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Abstract

The attention deficit hyperactive disorder (ADHD) is a neurophysiologic problem that is detrimental to children and their parents. Despite previous studies on the role of foods, preservatives and artificial colorings in ADHD this issue remains controversial. This investigation evaluated 26 children who meet the criteria for ADHD. Treatment with a multiple item elimination diet showed 19 children (73%) responded favorably, $P < .001$. On open challenge, all 19 children reacted to many foods, dyes, and/or preservatives. A double-blind placebo controlled food challenge (DBPCFC) was completed in 16 children. There was a significant improvement on placebo days compared with challenge days ($P = .003$). Atopic children with ADHD had a significantly higher response rate than the nonatopic group. This study demonstrates a beneficial effect of eliminating reactive foods and artificial colors in children with ADHD. Dietary factors may play a significant role in the etiology of the majority of children with ADHD.

http://www.ncbi.nlm.nih.gov/pubmed/8179235

“Behavioral changes in irritability, restlessness, and sleep disturbance are associated with the ingestion of tartrazine in some children. A dose response effect was observed.”

Journal Of Pediatrics • November 1994

Synthetic food coloring and behavior: a dose response effect in a double-blind, placebo-controlled, repeated-measures study

Author information

Rowe KS1, Rowe KJ.
Department of Pediatrics, University of Melbourne, Royal Children’s Hospital, Victoria, Australia

Abstract

OBJECTIVE

To establish whether there is an association between the ingestion of synthetic food colorings and behavioral change in children referred for assessment of “hyperactivity.”

PARTICIPANTS

From approximately 800 children referred to the Royal Children’s Hospital (Melbourne) for assessment of suspected hyperactivity, 200 were included in a 6-week open trial of a diet free of synthetic food coloring. The parents of 150 children reported behavioral improvement with the diet, and deterioration on the introduction of foods noted to contain synthetic coloring. A 30-item behavioral rating inventory was devised from an examination of the clinical histories of 50 suspected reactors. Thirty-four other children (23 suspected reactors, 11 uncertain reactors) and 20 control subjects, aged 2 to 14 years, were studied.

DESIGN

A 21-day, double-blind, placebo-controlled, repeated-measures study used each child as his or her own control. Placebo, or one of six dose levels of tartrazine (1, 2, 5, 10, 20, 50 mg), was administered randomly each morning, and behavioral ratings were recorded by parents at the end of each 24 hours.

RESULTS

The study identified 24 children as clear reactors (19 of 23 “suspected reactors,” 3 of 11 “uncertain reactors,” and 2 of 20 “control subjects”). They were irritable and restless and had sleep disturbance. Significant reactions were observed at all six dose levels. A dose response effect was obtained. With a dose increase greater than 10 mg, the duration of effect was prolonged.

CONCLUSION

Behavioral changes in irritability, restlessness, and sleep disturbance are associated with the ingestion of tartrazine in some children. A dose response effect was observed.

http://www.ncbi.nlm.nih.gov/pubmed/7965420

Pediatrics • May 1993

The mystery ingredients: sweeteners, flavorings, dyes, and preservatives in analgesic/antipyretic, antihistamine/decongestant, cough and cold, antidiarrheal, and liquid theophylline preparations

Author information

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Abstract

OBJECTIVE

Pharmaceutical preparations may contain a variety of excipients ("inert ingredients"). These excipients are generally inactive; however, rare adverse effects caused by excipients have been reported. Information about the excipients in a particular preparation is not readily available.

METHODS

The information about sweeteners, flavorings, dyes, and preservatives for the chewable and liquid preparations of over-the-counter and prescription products of antidiarrhea, cough and cold, antihistamine/decongestant, analgesic/antipyretic, and liquid theophylline medications was collected.

RESULTS

Information about excipients in 102 chewable and liquid preparations was compiled. An average preparation contained two sweeteners. Saccharin and sucrose were the most common sweeteners found--each was present in 52 preparations--followed by sorbitol, glucose, fructose, and others. For 36 of the 102 preparations, type of flavoring was not specified. In the remaining preparations, cherry was the most common flavoring, followed by vanilla and lemon. Twenty-one different dyes and coloring agents were used. Red dye No. 40 was the most common (42/102), followed by yellow No. 6 (27/102). Of the eight preservatives used, sodium benzoate and methylparabens were present in 42 and 27 of the preparations, respectively. Tables detailing these excipients and adverse effects reported are presented.

CONCLUSIONS

The tables should be helpful to physicians in selecting preparations containing different excipients when an adverse reaction occurs. The mandatory labeling of excipients in all pharmaceutical preparations is the only way that physicians and patients can be fully informed.

http://www.ncbi.nlm.nih.gov/pubmed/7682684

“In this study, we report two cases of unusual reactions to food additives (tartrazine and benzoates) involving mainly the central nervous system (headache, migraine, overactivity, concentration and learning difficulties, depression) and joints (arthralgias), confirmed with diet and double blind challenge.”

La Pediatria Medica e Chirurgica • January 1992

Unusual reactions to food additives

Author information
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Servizio di Allergologia, Clinica Pediatrica 3, Firenze, Italia

Abstract

The most important symptoms caused by food additives are urticaria and angioedema, but rhinitis, asthma and gastrointestinal disturbances are also reported. Only seldom food additives have been shown to induce symptoms in other organs such central nervous system or joints and with a sparse objective evidence. In this study, we report two cases of unusual reactions to food additives (tartrazine and benzoates) involving mainly the central nervous system (headache, migraine, overactivity, concentration and learning difficulties, depression) and joints (arthralgias), confirmed with diet and double blind challenge. The possible pathogenetic mechanisms are also discussed.

http://www.ncbi.nlm.nih.gov/pubmed/1579515

EATING AS AN INCONVENIENCE

This study is almost 25 years old. That's enough time to see generational effects. Some of the peer reviewed literature references damage seen in second and third generation mice and rats from various chemical assaults on their parents of one kind or another. The rising incidence of cancers, heart disease, diabetes, the virtual explosion in obesity (one researcher referred to the obesity ***pandemic***) and autoimmune disorders makes it crystal clear that something is very wrong. It's food drugs. Food, or what now passes for food in the United States, may hold more responsibility for every disease known to woman and man than any other single factor. Lack of a proper diet combined with regular, daily consumption of very small doses of a variety of neurotoxic, genotoxic, carcinogenic, obesogenic and estrogenic chemicals is probably the number one cause of all human species disorders. And if not the actual cause of a disease or disorder, it's the final physical assault that pushes us over the edge and destroys our immune system. They're coloring us to death to make cheap, nutrition-less foods look palatable. They're sweetening us to death because the food tastes terrible otherwise. Yet food is an area that we, the consumer, fully overlook habitually and in fact culturally. Have you seen people wolfing down a sandwich and fries at a Fast Food joint, gulping back a soda and rushing to get back to their desk before their 30 minute lunch is over? Our chemically altered food culture has relegated eating to an inconvenience and blindly accepts deadly chemical cocktails as a time-saving food convenience.

Pediatrics • March 1991

Sweeteners, flavorings, and dyes in antibiotic preparations

Kumar A1, Weatherly MR, Beaman DC.

Author information

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Abstract

Even though a variety of adverse effects caused by sweeteners, flavorings, and dyes in susceptible individuals have been reported, there is no good single reference with information about these substances in pediatric antimicrobials.

"Data on sweeteners, flavorings, and dyes in 91 antimicrobial preparations were collected. Sucrose was present in 74 (85%) of 87 preparations, followed by saccharin in 30 (34%) preparations. Mannitol, lactose, and sorbitol were each present in 7 preparations. None of the preparations were free of sweeteners. Thirty-four (37%) of 91 preparations did not specify the flavoring content. While cherry was the most common flavoring used, there were 25 other flavorings. Thirteen different dyes and coloring agents were used in these antimicrobials. Red dye no. 40 was present in 45% of preparations."

Tables detailing sweeteners, flavorings, and dyes in different groups of antimicrobials (amoxicillin, ampicillin, cephalosporins, erythromycin, penicillins, sulfonamides, and others) and adverse effects reported with these inert ingredients are presented. These tables should be helpful to physicians in selecting an antimicrobial containing a different sweetener and/or dye when an adverse reaction occurs.

http://www.ncbi.nlm.nih.gov/pubmed/2000275

“We performed an objective evaluation of 39 children whose behaviour was observed by their parents to improve on an artificial food additive free diet and to deteriorate with dietary lapses. In these children food colours were shown to have an adverse effect ...”

Archives Of Disease In Childhood • January 1990

Effect of artificial food colours on childhood behaviour

Author information

Pollock I1, Warner JO.
Heart and Lung Institute, Brompton Hospital, London

Abstract

We performed an objective evaluation of 39 children whose behaviour was observed by their parents to improve on an artificial food additive free diet and to deteriorate with dietary lapses. Only 19 children completed a double blind placebo controlled challenge study with artificial food colours. In these children food colours were shown to have an adverse effect on a daily Conners’ rating of behaviour, but most parents could not detect these changes. A pharmacological mechanism of food additive intolerance is proposed to explain these effects.

Full text with 24 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1792406/

“In some instances, an additive or dye in a food or drug may be responsible for the reaction.”

Postgrad Medicine • May 1989

Persistent urticaria caused by a common coloring agent

Author information
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Medical College of Wisconsin, Milwaukee

Abstract

As this case illustrates, foods or drugs may be ignored as possible causes of urticaria when they are not commonly accepted offenders or when they previously have been consumed with no adverse effect. In some instances, an additive or dye in a food or drug may be responsible for the reaction. In addition, a change of brands or dosage form of a drug may provoke urticaria or other reactions in sensitive individuals.

Urticaria

Urticaria, commonly referred to as hives, is a kind of skin rash notable for pale red, raised, itchy bumps. Hives may cause a burning or stinging sensation. They are frequently caused by allergic reactions; however, there are many nonallergic causes. Most cases of hives lasting less than six weeks (acute urticaria) are the result of an allergic trigger. Chronic urticaria (hives lasting longer than six weeks) is rarely due to an allergy. The majority of chronic hives cases have an unknown (idiopathic) cause. In perhaps more than 50% of patients with chronic idiopathic urticaria, it is caused by an autoimmune reaction.

http://www.ncbi.nlm.nih.gov/pubmed/2710728

“The findings raise the issue of whether the strict criteria for inclusion in studies concerned with ‘hyperactivity’ based on ‘attention deficit disorder’ may miss children who indicate behavioural changes associated with the ingestion of food colourings.”

Australian Paediatrics Journal • April 1988

Synthetic food colourings and ‘hyperactivity’: a double-blind crossover study

Author information

By KS Rowe
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Abstract

Of 220 children referred for suspected ‘hyperactivity’, 55 were subjected to a 6 week trial of the Feingold diet. Forty (72.7%) demonstrated improved behaviour and 26 (47.3%) remained improved following liberalization of the diet over a period of 3-6 months. The parents of 14 children claimed that a particular cluster of behaviours was associated with the ingestion of foods containing synthetic colourings. A double-blind crossover study, employing a single-subject repeated measures design was conducted, using eight of these children. Subjects were maintained on a diet free from synthetic additives and were challenged daily for 18 weeks with either placebo (during lead-in and washout periods) or 50 mg of either tartrazine or carmoisine, each for 2 separate weeks. Two significant reactors were identified whose behavioural pattern featured extreme irritability, restlessness and sleep disturbance. One of the reactors did not have inattention as a feature. The findings raise the issue of whether the strict criteria for inclusion in studies concerned with ‘hyperactivity’ based on ‘attention deficit disorder’ may miss children who indicate behavioural changes associated with the ingestion of food colourings. Moreover, for further studies, the need to construct a behavioural rating instrument specifically validated for dye challenge is suggested.

http://www.ncbi.nlm.nih.gov/pubmed/3395307

“The Restaurant syndromes can be caused by five major factors: food allergens, **sulfites, monosodium glutamate (MSG), tartrazine**, and scombroidosis (and other seafood poisoning).”

New England And Regional Allergy Proceedings • January 1987

The Restaurant Syndromes

By GA Settipane

Abstract

The Restaurant syndromes can be caused by five major factors: food allergens, sulfites, monosodium glutamate (MSG), tartrazine, and scombroidosis (and other seafood poisoning). A history of atopy and ingestion of known food allergens such as peanuts, egg, fish, and walnuts, together with positive results of skin tests or RAST to these foods, will favor a diagnosis of food allergy. Allergic reactions to peanuts have produced fatalities in minutes through an IgE mediated reaction. An extremely rapid onset (minutes) of symptoms consisting of flushing, bronchospasm and hypotension is consistent with a sulfite reaction. Burning, pressure, and tightness or numbness in the face, neck, and upper chest following ingestion of Chinese food favors a diagnosis of adverse reaction to MSG. Also, development of late onset bronchospasm (up to 14 hours) may be related to MSG reactions. Bronchospasm and urticaria in a patient with a history of aspirin intolerance suggests tartrazine sensitivity. If everyone ingesting a fish meal develops flushing, urticaria, pruritus, gastrointestinal complaints, or bronchospasm, this implies scombroidosis, ciguatera, or other seafood poisoning. Finally, severe headache or hypertension can result from ingestion of naturally occurring amines, such as tyramine (cheese, red wine) and phenylethylamine (chocolate). A double-blind oral challenge test may be the only way of confirming the diagnosis for most of the etiological factors of the Restaurant syndromes. The treatment of choice for acute reaction is epinephrine followed by antihistamine. Proper labeling and avoidance of these ingredients in sensitive individuals are the best preventive measures.

http://www.ncbi.nlm.nih.gov/pubmed/3302666

“Tartrazine, a common additive in foods and drugs, often causes adverse reactions such as recurrent urticaria, angioedema, and asthma and is frequently implicated in hyperkinesis.”

Journal Of Asthma • July 1985

Clinical spectrum of adverse reactions to tartrazine

By C. Collins-Williams

Abstract

Tartrazine, a common additive in foods and drugs, often causes adverse reactions such as recurrent urticaria, angioedema, and asthma and is frequently implicated in hyperkinesis. This paper summarizes the recent literature on the subject and outlines a practical approach for the practicing physician to diagnose and treat these patients in an optimal manner.

http://www.ncbi.nlm.nih.gov/pubmed/3894321

“From 4% to 14% of individuals with asthma or allergies or both and from 7% to 20% of persons who are sensitive to acetylsalicylic acid may react to this dye. The mechanism of such reactions is unknown. Pharmaceutical manufacturers and distributors were surveyed and a list was prepared of approximately 450 Canadian pharmaceuticals that contain tartrazine.”

Canadian Medical Association Journal • April 1982

Tartrazine: a potentially hazardous dye in Canadian drugs

By ME MacCara

Abstract

The literature was reviewed to determine the incidence of idiosyncratic reactions to tartrazine. From 4% to 14% of individuals with asthma or allergies or both and from 7% to 20% of persons who are sensitive to acetylsalicylic acid may react to this dye. The mechanism of such reactions is unknown. Pharmaceutical manufacturers and distributors were surveyed and a list was prepared of approximately 450 Canadian pharmaceuticals that contain tartrazine. The 53 pharmaceutical and manufacturers and distributors whose drug products do not contain this dye were also listed. It is recommended that information concerning the tartrazine content of drugs be included on package labels.

Full text with 28 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1862961/

Canadian Medical Association Journal • August 1976

Tartrazine-containing drugs

By W. R. Bartle

Abstract

Pharmaceutical manufacturers producing or distributing drugs in Canada were surveyed between December 1974 and March 1975 to determine which of their products contained tartrazine, a pyrazole aniline dye. A list of some 580 drug products of the 156 manufacturers who responded is presented for aid in managing the tartrazine-sensitive patients.

Full Text with references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1878658/

“After undergoing exhaustive studies and without being able to identify an offender, patients were submitted to oral provocation with different food additives—tartrazine, sunset yellow FCF, new coccine, erythrosine, sodium benzoate, 4-methyl hydroxybenzoate and acetylsalicylic acid—after 48 hours of exclusion from their diets of dyes, preservatives and salicylates. The results obtained reflect, at a global level, 57.89% of positivities for dyes, 34.21% for the benzoates and 7.81% for acetyl-salicylic acid.”

Allergologia et Immunopathologia • Madrid • July 1982

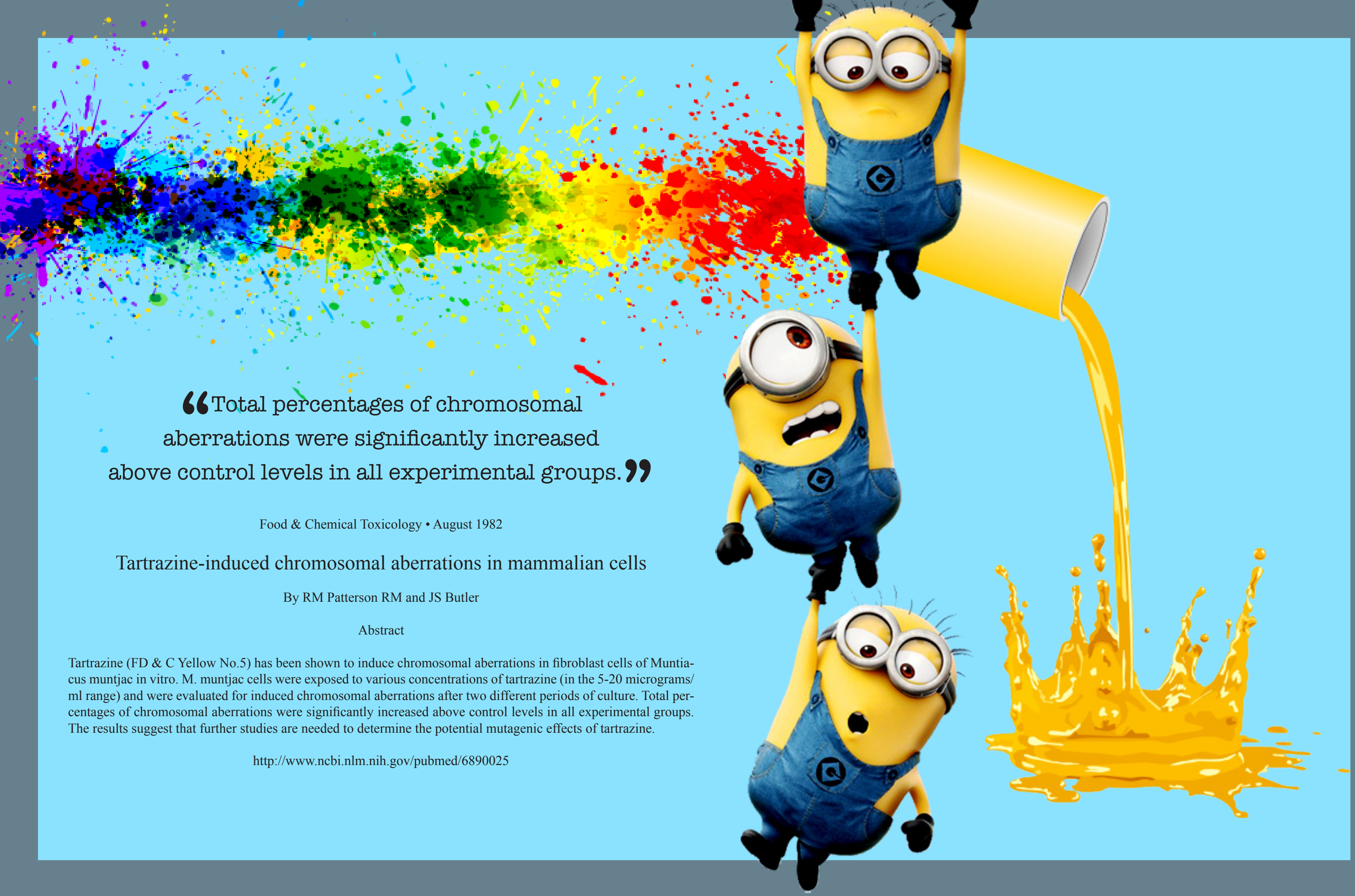
Dyes, preservatives and salicylates in the induction of food intolerance and/or hypersensitivity in children

Ibero M, Eseverri JL, Barroso C, Botey J.

Abstract

We present 25 patients, aged between 18 and 153 months, with clinical symptoms suggestive of allergy to food antigens. After undergoing exhaustive studies (including case histories, cutaneous tests for reactions to food antigen, peripheral eosinophils, secretory and humoral immunity, determination of total IgE and of specific RAST, exclusion-provocation diets) and without being able to identify an offender, patients were submitted to oral provocation with different food additives (tartrazine, sunset yellow FCF, new coccine, erythrosine, sodium benzoate, 4-methyl hydroxybenzoate and acetylsalicylic acid) after 48 hours of exclusion from their diets of dyes, preservatives and salicylates. The results obtained reflect, at a global level, 57.89% of positivities for dyes, 34.21% for the benzoates and 7.81% for acetyl-salicylic acid. The low incidence of crossed intolerance phenomena should be emphasized (32% of the patients). The disparity of our results with those of other authors could be due to the age of our patients, the clinical patterns they present and the dietary habits of different countries and regions.

http://www.ncbi.nlm.nih.gov/pubmed/6295125



“Total percentages of chromosomal aberrations were significantly increased above control levels in all experimental groups.”

Food & Chemical Toxicology • August 1982

Tartrazine-induced chromosomal aberrations in mammalian cells

By RM Patterson RM and JS Butler

Abstract

Tartrazine (FD & C Yellow No.5) has been shown to induce chromosomal aberrations in fibroblast cells of Muntiacus muntjac in vitro. M. muntjac cells were exposed to various concentrations of tartrazine (in the 5-20 micrograms/ml range) and were evaluated for induced chromosomal aberrations after two different periods of culture. Total percentages of chromosomal aberrations were significantly increased above control levels in all experimental groups. The results suggest that further studies are needed to determine the potential mutagenic effects of tartrazine.

http://www.ncbi.nlm.nih.gov/pubmed/6890025

“The symptoms of Chinese Restaurant Syndrome, although not hazardous, furthermore illustrate that the whole Acceptable Daily Intake cannot always be ingested as a single dose on an empty stomach with impunity.”

Archives Of Toxicology • Supplement • 1978

Food additives

By F. Berglund

Abstract

The use of additives to food fulfils many purposes, as shown by the index issued by the Codex Committee on Food Additives: Acids, bases and salts; Preservatives, Antioxidants and antioxidant synergists; Anticaking agents; Colours; Emulfifiers; Thickening agents; Flour-treatment agents; Extraction solvents; Carrier solvents; Flavours (synthetic); Flavour enhancers; Non-nutritive sweeteners; Processing aids; Enzyme preparations. Many additives occur naturally in foods, but this does not exclude toxicity at higher levels. Some food additives are nutrients, or even essential nutritents, e.g. NaCl. Examples are known of food additives causing toxicity in man even when used according to regulations, e.g. cobalt in beer. In other instances, poisoning has been due to carry-over, e.g. by nitrate in cheese whey - when used for artificial feed for infants. Poisonings also occur as the result of the permitted substance being added at too high levels, by accident or carelessness, e.g. nitrite in fish. Finally, there are examples of hypersensitivity to food additives, e.g. to tartrazine and other food colours. The toxicological evaluation, based on animal feeding studies, may be complicated by impurities, e.g. orthotoluene-sulfonamide in saccharin; by transformation or disappearance of the additive in food processing in storage, e.g. bisulfite in raisins; by reaction products with food constituents, e.g. formation of ethylurethane from diethyl pyrocarbonate; by metabolic transformation products, e.g. formation in the gut of cyclohexylamine from cyclamate. Metabolic end products may differ in experimental animals and in man: guanylic acid and inosinic acid are metabolized to allantoin in the rat but to uric acid in man. The magnitude of the safety margin in man of the Acceptable Daily Intake (ADI) is not identical to the “safety factor” used when calculating the ADI. The symptoms of Chinese Restaurant Syndrome, although not hazardous, furthermore illustrate that the whole ADI cannot always be ingested as a single dose on an empty stomach with impunity.

http://www.ncbi.nlm.nih.gov/pubmed/277126

“Tartrazine did appear to exert more general signs of toxicity in the offspring—namely, depressed body weight, an apparent reduction in thymus weight, and a slight elevation of red blood cells and hemoglobin.”

Journal Of Toxicology And Environmental Health • May 1977

Tartrazine and the developing nervous system of rats

By TJ Sobotka, RE Brodie and SL Spaid

Abstract

Rat dams were exposed to the artificial food color tartrazine (FD&C Yellow no. 5) at dietary levels of 0, 1, and 2% during gestation and lactation. The experimental offspring were continued on the same diets for approximately 3 months after weaning. No adverse physical or behavioral effects were noted in the dams. Fetal development and postnatal viability of the offspring were also normal. The only effect on postnatal development of the central nervous system (CNS) was a small transient change in neuromotor clinging ability of female offspring. The limited effect of tartrazine on the CNS was further evidenced by the facts that (1) the neurobehavioral profiles of the experimental weanlings revealed no significant abnormalities, and (2) morphochemical analysis of brain tissue, as well as brain weights, revealed no abnormalities. Tartrazine did appear to exert more general signs of toxicity in the offspring—namely, depressed body weight, an apparent reduction in thymus weight, and a slight elevation of red blood cells and hemoglobin.

http://www.ncbi.nlm.nih.gov/pubmed/864790

Journal Of Nutrition • May 1977

Effects of diet on growth and survival of rats fed toxic levels of tartrazine (FD & C Yellow No. 5) and sunset yellow FCF (FD & C Yellow No. 6)

By BH Ershoff

Tests were conducted on the effects of diet on the response of immature male rats to massive doses of tartrazine (FD&C Yellow No.5) and Sunset Yellow FCF (FD&C Yellow No. 6). When incorporated at a 5% level in a stock diet, tartrazine and Sunset Yellow FCF had no grossly observable toxic effects. When fed with a purified diet, however, both tartrazine and Sunset Yellow FCF at 5% level in the diet resulted in a marked retardation in growth, an unthrifty appearance of the fur and death of 50% or more of the rats within an experimental period of 14 days. The toxic effects obtained by feeding the latter diets were counteracted by the concurrent feeding of blond psyllium seed powder, carrot root powder, alfalfa leaf meal and wheat bran. Supplements of the known nutrients had little if any protective effect. Supplements of purified cellulose were without protective effect for the rats fed tartrazine but had a moderate protective effect for those fed Sunset Yellow FCF.

http://www.ncbi.nlm.nih.gov/pubmed/859044

http://www.ncbi.nlm.nih.gov/pubmed/859044

“... both tartrazine and Sunset Yellow FCF at 5% level in the diet resulted in a marked retardation in growth, an unthrifty appearance of the fur and death of 50% or more of the rats within an experimental period of 14 days.

The toxic effects obtained by feeding the latter diets were counteracted by the concurrent feeding of blond psyllium seed powder, carrot root powder, alfalfa leaf meal and wheat bran.”

Applied Microbiology • August 1975

Microwave sanitization of color additives used in cosmetics: feasibility study

Jasnow SB, Smith JL.

Abstract

"Microwave exposure has been explored as a method of microbiologically sanitizing color additives used in cosmetic products. Selected microbiologically unacceptable cosmetic color additives, D&C red no. 7 Ca lake (certified synthetic organic color), carmine (natural organic color not subject to certification), and chromium hydroxide green (inorganic color not subject to certification), were submitted to microwave exposure. Gram-negative bacteria were eliminated, as verified by enrichment procedures, and levels of gram-positive bacteria were reduced. Generally, analytical and dermal safety studies indicated no significant alterations in physical, chemical, and toxicological properties of the colors. Sanitization was also successfully performed on other colors (D&C red no. 9 Ba lake, D&C red no. 12 Ba lake, D&C green no. 5, and FD&C red no. 4); initial physical and chemical tests were satisfactory. Results indicated that this method of sanitization is feasible and warrants further investigation."

http://www.ncbi.nlm.nih.gov/pubmed/1164010

CHAPTER TEN

Monsanto's Glyphosate Herbicide & RoundUp

The Peer Review

This chapter on Glyphosate, which is a food drug since it's found on and in almost all conventional produce, was taken from my eBook titled, "Bullet Proof," which is linked on the next to the last page of this eBook and has over 500 additional peer reviewed reports, studies and links on glyphosate and its extraordinary propensity to cause human diseases and disorders.

Glyphosate now shows up in the blood, urine and breast milk of over 90% of those tested at levels varying from worrisome to dangerous. Glyphosate is responsible for almost every disease known to the human species and it has a similar impact on insects, all mammals, birds, reptiles and soil bacteria. It's deadly to everything it comes into contact with. Repeated contact is not advised. Read the peer review. Many conventional, non-GMO crops are sprayed with glyphosate during the last 1-3 weeks of growth, just prior to harvest. They're drenched with glyphosate. Glyphosate is an herbicide, not a pesticide, and it desiccates any non-GMO crops just like it desiccates weeds. This means it totally dehydrates the conventional non-GMO crop it's sprayed on so that the crop quickly dies. This procedure dramatically reduces the costs of harvesting when the various food crops have been desiccated or dehydrated prior to harvest. Many conventional food crops, especially wheat and corn, but many crops in general are desiccated before harvest with glyphosate. It's easier to harvest dead plants/stalks with still viable fruits and vegetables attached than it is to harvest green plant stalks that are strong and full of life.

Monsanto spent millions of dollars on a "dessication benefits" marketing project for farmers across the USA with glossy sales brochures and high powered sales reps to manage dessication training programs. The purchase of glyphosate for desiccation alone increased significantly and that segment of total glyphosate sales remains a high marketing priority. Glyphosate, like Bisphenol A and other heavily used and manufactured products—compounds manufactured in the millions of tons—is in the air we breathe, the soil we walk on and dig in (*the dirt our kids play in*) and the dust in our homes.

Environmental Working Group (EWG) lists conventional apples as the most egregious offender with as many as 14 different pesticides, herbicides and fungicides found on conventionally grown apples. Eating organic may save your life.

“Both POEA and glyphosate caused lung hemorrhage and lung epithelial cell damage”

The oral and intratracheal toxicities of ROUNDUP and its components to rats

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Abstract

The toxicities of ROUNDUP and its component chemicals, glyphosate (N-phosphonomethylglycine) and polyoxyethyleneamine (POEA), were determined at 0, 1, 3, 6 and 24 h following administration to rats. The intratracheal administration of glyphosate (0.2 g/kg), POEA (0.1 g/kg), a mixture of glyphosate (0.2 g/kg) + POEA (0.1 g/kg), or ROUNDUP (containing 0.2 g/kg glyphosate and 0.1 g/kg POEA) elicited immediate respiratory effects which were more severe and which lasted longer in the groups receiving the POEA-containing preparations than in the glyphosate alone group. By 1 h, all test preparations had caused deaths, but more occurred from the POEA-containing preparations than from glyphosate. The po administration of POEA (1 g/kg), the mixture of glyphosate (2 g/kg) +POEA (1 g/kg), or ROUNDUP (containing 2 g/kg glyphosate and 1 g/kg POEA) produced diarrhea and blood-stained weeping from noses. Death was only seen from POEA at 24 h. Glyphosate (2 g/kg po) produced transient diarrhea without nose bleeds; POEA caused diarrhea at 1 h; and the mixture of POEA + glyphosate produced diarrhea later that increased in severity with time. Bloody nose secretions were seen only with the preparations that contained POEA. No deaths, respiratory effects or bloody nose secretions occurred in controls given saline. Both POEA and glyphosate caused lung hemorrhages and lung epithelial cell damage with po or intratracheal exposures. These results indicate POEA and preparations that contained POEA were more toxic than glyphosate.

http://www.ncbi.nlm.nih.gov/pubmed/9167243

“... the concordance of the effects induced by low concentrations of Roundup on HTC cells suggests that the presence of Roundup residues could be one of the factors interfering with multiple metabolic pathways ...”

Hepatoma tissue culture (HTC) cells as a model for investigating the effects of low concentrations of herbicide on cell structure and function

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Abstract

Previous studies on mice fed genetically modified (GM) soybean demonstrated modifications of the mitochondrial functions and of the transcription/splicing pathways in hepatocytes. The cause(s) of these alterations could not be conclusively established but, since the GM soybean used is tolerant to glyphosate and was treated with the glyphosate-containing herbicide Roundup , the possibility exists that the effects observed may be due to herbicide residues. In order to verify this hypothesis, we treated HTC cells with 1-10mM Roundup and analysed cellular features by flow cytometry, fluorescence and electron microscopy. Under these experimental conditions, the death rate and the general morphology of HTC cells were not affected, as well as most of the cytoplasmic organelles. However, in HTC-treated cells, lysosome density increased and mitochondrial membranes modified indicating a decline in the respiratory activity. Moreover, nuclei underwent morpho-functional modifications suggestive of a decreased transcriptional/splicing activity. Although we cannot exclude that other factors than the presence of the herbicide residues could be responsible for the cellular modifications described in GM-fed mice, the concordance of the effects induced by low concentrations of Roundup on HTC cells suggests that the presence of Roundup residues could be one of the factors interfering with multiple metabolic pathways.

http://www.ncbi.nlm.nih.gov/pubmed/18835430

“In these results, we argue that modified Bt toxins are not inert on non-target human cells, and that they can present combined side-effects with other residues of pesticides specific to GM plants”

Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidal toxins alone or with a glyphosate-based herbicide

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Abstract

The study of combined effects of pesticides represents a challenge for toxicology. In the case of the new growing generation of genetically modified (GM) plants with stacked traits, glyphosate-based herbicides (like Roundup) residues are present in the Roundup-tolerant edible plants (especially corns) and mixed with modified Bt insecticidal toxins that are produced by the GM plants themselves. The potential side effects of these combined pesticides on human cells are investigated in this work. Here we have tested for the very first time Cry1Ab and Cry1Ac Bt toxins (10 ppb to 100 ppm) on the human embryonic kidney cell line 293, as well as their combined actions with Roundup, within 24 h, on three biomarkers of cell death: measurements of mitochondrial succinate dehydrogenase, adenylate kinase release by membrane alterations and caspase 3/7 inductions. Cry1Ab caused cell death from 100 ppm. For Cry1Ac, under such conditions, no effects were detected. The Roundup tested alone from 1 to 20 000 ppm is necrotic and apoptotic from 50 ppm, far below agricultural dilutions (50% lethal concentration 57.5 ppm). The only measured significant combined effect was that Cry1Ab and Cry1Ac reduced caspases 3/7 activations induced by Roundup; this could delay the activation of apoptosis. There was the same tendency for the other markers. In these results, we argue that modified Bt toxins are not inert on nontarget human cells, and that they can present combined side-effects with other residues of pesticides specific to GM plants.

http://www.ncbi.nlm.nih.gov/pubmed/22337346

“Sea urchin embryos were used to test the worldwide used pesticide Roundup that contains glyphosate as the active herbicide agent; it was shown to activate the DNA-damage checkpoint of the first cell cycle of development of cancer”

Sea urchin embryo, DNA-damaged cell cycle checkpoint and the mechanisms initiating cancer development

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Abstract

Cell division is an essential process for heredity, maintenance and evolution of the whole living kingdom. Sea urchin early development represents an excellent experimental model for the analysis of cell cycle checkpoint mechanisms since embryonic cells contain a functional DNA-damage checkpoint and since the whole sea urchin genome is sequenced. The DNA-damaged checkpoint is responsible for an arrest in the cell cycle when DNA is damaged or incorrectly replicated, for activation of the DNA repair mechanism, and for commitment to cell death by apoptosis in the case of failure to repair. New insights in cancer biology lead to two fundamental concepts about the very first origin of cancerogenesis. Cancers result from dysfunction of DNA-damaged checkpoints and cancers appear as a result of normal stem cell (NCS) transformation into a cancer stem cell (CSC). The second aspect suggests a new definition of “cancer”, since CSC can be detected well before any clinical evidence. Since early development starts from the zygote, which is a primary stem cell, sea urchin early development allows analysis of the early steps of the cancerization process. Although sea urchins do not develop cancers, the model is alternative and complementary to stem cells which are not easy to isolate, do not divide in a short time and do not divide synchronously. In the field of toxicology and incidence on human health, the sea urchin experimental model allows assessment of cancer risk from single or combined molecules long before any epidemiologic evidence is available. Sea urchin embryos were used to test the worldwide used pesticide Roundup that contains glyphosate as the active herbicide agent; it was shown to activate the DNA-damage checkpoint of the first cell cycle of development. The model therefore allows considerable increase in risk evaluation of new products in the field of cancer and offers a tool for the discovery of molecular markers for early diagnostic in cancer biology. Prevention and early diagnosis are two decisive elements of human cancer therapy.

http://www.ncbi.nlm.nih.gov/pubmed/18157084

“In this study we observed in two mammalian species (rats and rabbits) direct cardiac electrophysiological changes, conduction blocks and arrhythmias among GBH-mediated effects.”

Glyphosate-Based Herbicides Potently Affect Cardiovascular System in Mammals: Review of the Literature.

Author information
by Gress S1, Lemoine S, Séralini GE, Puddu PE.
Cardiovascular Toxicology • September 23, 2014

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Abstract

In glyphosate (G)-based herbicides (GBHs), the declared active principle G is mixed with several adjuvants that help it to penetrate the plants’ cell membranes and its stabilization and liposolubility. Its utilization is growing with genetically modified organisms engineered to tolerate GBH. Millions of farmers suffer poisoning and death in developing countries, and occupational exposures and suicide make GBH toxicity a worldwide concern. As GBH is found in human plasma, widespread hospital facilities for measuring it should be encouraged. Plasma determination is an essential prerequisite for risk assessment in GBH intoxication. Only when standard ECGs were performed, at least one abnormal ECG was detected in the large majority of cases after intoxication. QTc prolongation and arrhythmias along with first-degree atrioventricular block were observed after GBH intoxication. Thus, life-threatening arrhythmias might be the cause of death in GBH intoxication. Cardiac cellular effects of GBH were reviewed along with few case reports in men and scanty larger studies. We observed in two mammalian species (rats and rabbits) direct cardiac electrophysiological changes, conduction blocks and arrhythmias among GBH-mediated effects. Plasmatic (and urine) level determinations of G and electrocardiographic Holter monitoring seem warranted to ascertain whether cardiovascular risk among agro-alimentary workers might be defined.

http://www.ncbi.nlm.nih.gov/pubmed/25245870

“According to our results, a glyphosate-based herbicide inhibits proliferation and differentiation in this mammalian cell line and induces apoptosis suggesting GF-mediated cellular damage. Thus, Glyphosate is a potential risk factor for human health and the environment”

A commercial formulation of glyphosate inhibits proliferation and differentiation to adipocytes and induces apoptosis in 3T3-L1 fibroblasts

Author information
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Abstract

Glyphosate-based herbicides are extensively used for weed control all over the world. Therefore, it is important to investigate the putative toxic effects of these formulations which include not only glyphosate itself but also surfactants that may also be toxic. 3T3-L1 fibroblasts are a useful tool to study adipocyte differentiation, this cell line can be induced to differentiate by addition of a differentiation mixture containing insulin, dexamethasone and 3-isobutyl-1-methylxanthine. We used this cell line to investigate the effect of a commercial formulation of glyphosate (GF) on proliferation, survival and differentiation. It was found that treatment of exponentially growing cells with GF for 48h inhibited proliferation in a dose-dependent manner. In addition, treatment with GF dilution 1:2000 during 24 or 48h inhibited proliferation and increased cell death, as evaluated by trypan blue-exclusion, in a time-dependent manner. We showed that treatment of 3T3-L1 fibroblasts with GF increased caspase-3 like activity and annexin-V positive cells as evaluated by flow cytometric analysis, which are both indicative of induction of apoptosis. It was also found that after the removal of GF, remaining cells were able to restore proliferation. On the other hand, GF treatment severely inhibited the differentiation of 3T3-L1 fibroblasts to adipocytes. According to our results, a glyphosate-based herbicide inhibits proliferation and differentiation in this mammalian cell line and induces apoptosis suggesting GF-mediated cellular damage. Thus, GF is a potential risk factor for human health and the environment.

http://www.ncbi.nlm.nih.gov/pubmed/22546541

“These results indicated that low and environmentally relevant concentrations of glyphosate possessed estrogenic activity. Glyphosate exerted proliferative effects only in human hormone-dependent breast cancer, T47D cells”

Glyphosate induces human breast cancer cell growth via estrogen receptors

by Thongprakaisang, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J.

Abstract

Glyphosate is an active ingredient of the most widely used herbicide and it is believed to be less toxic than other pesticides. However, several recent studies showed its potential adverse health effects to humans as it may be an endocrine disruptor. This study focuses on the effects of pure glyphosate on estrogen receptors (ERs) mediated transcriptional activity and their expressions. Glyphosate exerted proliferative effects only in human hormone-dependent breast cancer, T47D cells, but not in hormone-independent breast cancer, MDA-MB231 cells, at 10ß¹² to 10ßM in estrogen withdrawal condition. The proliferative concentrations of glyphosate that induced the activation of estrogen response element (ERE) transcription activity were 5-13 fold of control in T47D-KBluc cells and this activation was inhibited by an estrogen antagonist, ICI 182780, indicating that the estrogenic activity of glyphosate was mediated via ERs. Furthermore, glyphosate also altered both ERß and ß expression. These results indicated that low and environmentally relevant concentrations of glyphosate possessed estrogenic activity. Glyphosate-based herbicides are widely used for soybean cultivation, and our results also found that there was an additive estrogenic effect between glyphosate and genistein, a phytoestrogen in soybeans. However, these additive effects of glyphosate contamination in soybeans need further animal study.

http://www.ncbi.nlm.nih.gov/pubmed/23756170

“Unfortunately, the study carried out by Swedish oncologists in 2001 showed that glyphosate may induce cancer of the lymphatic system. The results of the Swedish study have changed our opinion about the “safety” of this herbicide.”

Glyphosate: a non-toxic pesticide?

by Pieniazek D1, Bukowska B, Duda W.
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Abstract

Glyphosate is currently the most commonly applied herbicide and its use is still growing. Nowadays, over 50 commercial preparations containing this compound are used, and these formulations are much more toxic than their active compound, glyphosate, owing to the presence of many surfactants and carrier compounds. Toxicological investigations provide evidence that glyphosate is an extremely “safe” herbicide for animals. This is why its use in agriculture is universal. In June 1991, the Environmental Protection Agency (EPA) categorized this compound into class E (according to EPA there are five categories of carcinogenicity), which means that it is probably not carcinogenic to humans. Unfortunately, the study carried out by Swedish oncologists in 2001 showed that glyphosate may induce cancer of the lymphatic system. The results of the Swedish study have changed our opinion about “safety” of this herbicide. Investigations concerning both its accumulation and toxic effect in animals and plants are now under way in many laboratories.

http://www.ncbi.nlm.nih.gov/pubmed/15055003

“A deregulation of programmed cell death mechanisms in human epidermis leads to skin pathologies. We previously showed that glyphosate, an extensively used herbicide, provoked cytotoxic effects on cultured human keratinocytes. At the same time, we showed that the glyphosate-induced mitochondrial membrane potential disruption could be a cause of apoptosis in keratinocyte cultures”

A step further toward glyphosate-induced epidermal cell death: involvement of mitochondrial and oxidative mechanisms

Author information

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Abstract

A deregulation of programmed cell death mechanisms in human epidermis leads to skin pathologies. We previously showed that glyphosate, an extensively used herbicide, provoked cytotoxic effects on cultured human keratinocytes, affecting their antioxidant capacities and impairing morphological and functional cell characteristics. The aim of the present study, carried out on the human epidermal cell line HaCaT, was to examine the part of apoptosis plays in the cytotoxic effects of glyphosate and the intracellular mechanisms involved in the apoptotic events. We have conducted different incubation periods to reveal the specific events in glyphosate-induced cell death. We observed an increase in the number of early apoptotic cells at a low cytotoxicity level (15%), and then, a decrease, in favor of late apoptotic and necrotic cell rates for more severe cytotoxicity conditions. At the same time, we showed that the glyphosate-induced mitochondrial membrane potential disruption could be a cause of apoptosis in keratinocyte cultures.

http://www.ncbi.nlm.nih.gov/pubmed/22522424

“The herbicide glyphosate reduces plant growth and causes plant death by inhibiting the biosynthesis of aromatic amino acids”

Impairment of carbon metabolism induced by the herbicide glyphosate

Author information

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Abstract

The herbicide glyphosate reduces plant growth and causes plant death by inhibiting the biosynthesis of aromatic amino acids. The objective of this work was to determine whether glyphosate-treated plants show a carbon metabolism pattern comparable to that of plants treated with herbicides that inhibit branched-chain amino acid biosynthesis. Glyphosate-treated plants showed impaired carbon metabolism with an accumulation of carbohydrates in the leaves and roots. The growth inhibition detected after glyphosate treatment suggested impaired metabolism that impedes the utilization of available carbohydrates or energy at the expected rate. These effects were common to both types of amino acid biosynthesis inhibitors. Under aerobic conditions, ethanolic fermentative metabolism was enhanced in the roots of glyphosate-treated plants. This fermentative response was not related to changes in the respiratory rate or to a limitation of the energy charge. This response, which was similar for both types of herbicides, might be considered a general response to stress conditions.

http://www.ncbi.nlm.nih.gov/pubmed/21944839

“We observed in two mammalian species (rats and rabbits) direct cardiac electrophysiological changes, conduction blocks and arrhythmias among Glyphosate Based Herbicide-mediated effects.”

Glyphosate-Based Herbicides Potently Affect Cardiovascular System in Mammals: Review of the Literature

Author information

by Gress S1, Lemoine S, Séralini GE, Puddu PE.
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Abstract

In glyphosate (G)-based herbicides (GBHs), the declared active principle G is mixed with several adjuvants that help it to penetrate the plants’ cell membranes and its stabilization and liposolubility. Its utilization is growing with genetically modified organisms engineered to tolerate GBH. Millions of farmers suffer poisoning and death in developing countries, and occupational exposures and suicide make GBH toxicity a worldwide concern. As GBH is found in human plasma, widespread hospital facilities for measuring it should be encouraged. Plasma determination is an essential prerequisite for risk assessment in GBH intoxication. Only when standard ECGs were performed, at least one abnormal ECG was detected in the large majority of cases after intoxication. QTc prolongation and arrhythmias along with first-degree atrioventricular block were observed after GBH intoxication. Thus, life-threatening arrhythmias might be the cause of death in GBH intoxication. Cardiac cellular effects of GBH were reviewed along with few case reports in men and scanty larger studies. We observed in two mammalian species (rats and rabbits) direct cardiac electrophysiological changes, conduction blocks and arrhythmias among GBH-mediated effects. Plasmatic (and urine) level determinations of G and electrocardiographic Holter monitoring seem warranted to ascertain whether cardiovascular risk among agro-alimentary workers might be defined.

http://www.ncbi.nlm.nih.gov/pubmed/25245870

“The results support the possibility that mixtures of glyphosate and TN-20 aggravate mitochondrial damage and induce apoptosis and necrosis. Throughout this process, TN-20 seems to disrupt the integrity of the cellular barrier to glyphosate uptake, promoting glyphosate-mediated toxicity”

Mixtures of glyphosate and surfactant TN20 accelerate cell death via mitochondrial damage-induced apoptosis and necrosis

Author information

byKim YH1, Hong JR, Gil HW, Song HY, Hong SY
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Abstract

Glyphosate, a common herbicide, is not toxic under normal exposure circumstances. However, this chemical, when combined with a surfactant, is cytotoxic. In this study, the mechanism of the additive effect of glyphosate and TN-20, a common surfactant in glyphosate herbicides, was investigated. After exposure of rat H9c2 cells to glyphosate and TN-20 mixtures, following assays were performed: flow cytometry to determine the proportion of cells that underwent apoptosis and necrosis; western blotting to determine expression of mitochondrial proteins (Bcl-2 and Bax); immunological methods to evaluate translocation of cytochrome C; luminometric measurements to determine activity of caspases 3/7 and 9; and tetramethyl rhodamine methyl ester assay to measure mitochondrial membrane potentials. Bcl-1 intensity decreased while Bax intensity increased with exposure to increasing TN-20 and/or glyphosate concentrations. Caspase activity increased and mitochondrial membrane potential decreased only when the cells were exposed to a mixture of both TN-20 and glyphosate, but not after exposure to either one of these compounds. The results support the possibility that mixtures of glyphosate and TN-20 aggravate mitochondrial damage and induce apoptosis and necrosis. Throughout this process, TN-20 seems to disrupt the integrity of the cellular barrier to glyphosate uptake, promoting glyphosate-mediated toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/23099315

“This study, for the first time, provides evidence for the mechanism of glyphosate-induced occupational lung disease.”

Glyphosate-rich air samples induce IL-33, TSLP and generate IL-13 dependent airway inflammation.

by Kumar S1, Khodoun M2, Kettleson EM1, McKnight C3, Reponen T1, Grinshpun SA1, Adhikari A4.

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Abstract

Several low weight molecules have often been implicated in the induction of occupational asthma. Glyphosate, a small molecule herbicide, is widely used in the world. There is a controversy regarding a role of glyphosate in developing asthma and rhinitis among farmers, the mechanism of which is unexplored. The aim of this study was to explore the mechanisms of glyphosate induced pulmonary pathology by utilizing murine models and real environmental samples. C57BL/6, TLR4-/-, and IL-13-/- mice inhaled extracts of glyphosate-rich air samples collected on farms during spraying of herbicides or inhaled different doses of glyphosate and ovalbumin. The cellular response, humoral response, and lung function of exposed mice were evaluated. Exposure to glyphosate-rich air samples as well as glyphosate alone to the lungs increased: eosinophil and neutrophil counts, mast cell degranulation, and production of IL-33, TSLP, IL-13, and IL-5. In contrast, in vivo systemic IL-4 production was not increased. Co-administration of ovalbumin with glyphosate did not substantially change the inflammatory immune response. However, IL-13-deficiency resulted in diminished inflammatory response but did not have a significant effect on airway resistance upon methacholine challenge after 7 or 21 days of glyphosate exposure. Glyphosate-rich farm air samples as well as glyphosate alone were found to induce pulmonary IL-13-dependent inflammation and promote Th2 type cytokines, but not IL-4 for glyphosate alone. This study, for the first time, provides evidence for the mechanism of glyphosate-induced occupational lung disease.

http://www.ncbi.nlm.nih.gov/pubmed/25172162

“The results showed that glyphosate can induce harmful effects on reproductive parameters in D. rerio and that this change would Reduce the fertility rate of these animals.”

Effect of glyphosate on the sperm quality of zebrafish

by Danio rerio.Lopes FM1, Varela Junior AS2, Corcini CD3, da Silva AC4, Guazzelli VG5, Tavares G6, da Rosa

Abstract

Glyphosate is a systemic, non-selective herbicide widely used in agriculture worldwide. It acts as an inhibitor of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase by interrupting the synthesis of essential aromatic amino acids. This pathway is not present in animals, although some studies have shown that the herbicide glyphosate can affect fish reproduction. In this study, the effect of glyphosate on sperm quality of the fish Danio rerio was investigated after 24 and 96 h of exposure at concentrations of 5mg/L and 10mg/L. The spermatic cell concentration, sperm motility and motility period were measured employing conventional microscopy. The mitochondrial functionality, membrane integrity and DNA integrity were measured by fluorescence microscopy using specific probes. No significant differences in sperm concentration were observed; however, sperm motility and the motility period were reduced after exposure to both glyphosate concentrations during both exposure periods. The mitochondrial functionality and membrane and DNA integrity were also reduced at the highest concentration during both exposure periods. The results showed that glyphosate can induce harmful effects on reproductive parameters in D. rerio and that this change would reduce the fertility rate of these animals:

http://www.ncbi.nlm.nih.gov/pubmed/25089920

“Roundup™ was among the most toxic herbicides and insecticides tested. Most importantly, 8 formulations out of 9 were up to one thousand times more toxic than their active principles.”

Major pesticides are more toxic to human cells than their declared active principles

Mesnage R1, Defarge N1, Spiroux de Vendômois J2, Séralini GE1.

Author information

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2CRIIGEN, 40 rue Monceau, 75008 Paris, France.

Abstract

Pesticides are used throughout the world as mixtures called formulations. They contain adjuvants, which are often kept confidential and are called inerts by the manufacturing companies, plus a declared active principle, which is usually tested alone. We tested the toxicity of 9 pesticides, comparing active principles and their formulations, on three human cell lines (HepG2, HEK293, and JEG3). Glyphosate, isoproturon, fluroxypyr, pirimicarb, imidacloprid, acetamiprid, tebuconazole, epoxiconazole, and prochloraz constitute, respectively, the active principles of 3 major herbicides, 3 insecticides, and 3 fungicides. We measured mitochondrial activities, membrane degradations, and caspases 3/7 activities. Fungicides were the most toxic from concentrations 300-600 times lower than agricultural dilutions, followed by herbicides and then insecticides, with very similar profiles in all cell types. Despite its relatively benign reputation, Roundup was among the most toxic herbicides and insecticides tested. Most importantly, 8 formulations out of 9 were up to one thousand times more toxic than their active principles. Our results challenge the relevance of the acceptable daily intake for pesticides because this norm is calculated from the toxicity of the active principle alone. Chronic tests on pesticides may not reflect relevant environmental exposures if only one ingredient of these mixtures is tested alone:

http://www.ncbi.nlm.nih.gov/pubmed/24719846

“Although glyphosate alone does not cause an epidemic of chronic kidney disease, it seems to have acquired the ability to destroy the renal tissues of thousands of farmers when it forms complexes with a localized geoenvironmental factor (water hardness) and nephrotoxic metals.”

Glyphosate, hard water and nephrotoxic metals: are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka?

by Jayasumana C1, Gunatilake S2, Senanayake P3.

Author information

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Abstract

The current chronic kidney disease epidemic, the major health issue in the rice paddy farming areas in Sri Lanka has been the subject of many scientific and political debates over the last decade. Although there is no agreement among scientists about the etiology of the disease, a majority of them has concluded that this is a toxic nephropathy. None of the hypotheses put forward so far could explain coherently the totality of clinical, biochemical, histopathological findings, and the unique geographical distribution of the disease and its appearance in the mid-1990s. A strong association between the consumption of hard water and the occurrence of this special kidney disease has been observed, but the relationship has not been explained consistently. Here, we have hypothesized the association of using glyphosate, the most widely used herbicide in the disease endemic area and its unique metal chelating properties. The possible role played by glyphosate-metal complexes in this epidemic has not been given any serious consideration by investigators for the last two decades. Furthermore, it may explain similar kidney disease epidemics observed in Andra Pradesh (India) and Central America. Although glyphosate alone does not cause an epidemic of chronic kidney disease, it seems to have acquired the ability to destroy the renal tissues of thousands of farmers when it forms complexes with a localized geo environmental factor (hardness) and nephrotoxic metals:

http://www.ncbi.nlm.nih.gov/pubmed/24562182

“These results confirm that Glyphosate formulations have adjuvants working together with the active ingredient and causing toxic effects that are not seen with acid glyphosate”

Glyphosate commercial formulation causes cytotoxicity, oxidative effects, and apoptosis on human cells: differences with its active ingredient

by Chaufan G1, Coalova I, Ríos de Molina Mdel C.

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Abstract

In the present study, the effects on oxidative balance and cellular end points of glyphosate, aminomethylphosphonic acid (AMPA), and a glyphosate formulation (G formulation) were examined in HepG2 cell line, at dilution levels far below agricultural recommendations. Our results show that G formulation had toxic effects while no effects were found with acid glyphosate and AMPA treatments. Glyphosate formulation exposure produced an increase in reactive oxygen species, nitrotyrosine formation, superoxide dismutase activity, and glutathione (GSH) levels, while no effects were observed for catalase and GSH-S-transferase activities. Also, G formulation triggered caspase 3/7 activation and hence induced apoptosis pathway in this cell line. Aminomethylphosphonic acid exposure produced an increase in GSH levels while no differences were observed in other antioxidant parameters. No effects were observed when the cells were exposed to acid glyphosate. These results confirm that G formulations have adjuvants working together with the active ingredient and causing toxic effects that are not seen with acid glyphosate:

http://www.ncbi.nlm.nih.gov/pubmed/24434723

“It has been shown that glyphosate remains in the soil and can reach people by spreading along with groundwater. Based on numerous studies it was noted that commercial formulations of glyphosate exhibit higher toxicity than that of the active substance itself. The impact of glyphosate on oxygen reactive species formation, changes in redox system and the effect on necrosis and apoptosis in various types of cells was shown.”

Glyphosate and its Formulations
Toxicity, Occupational and Environmental Exposure

by Kwiatkowska M1, Pawes J2, Bukowska B2.

Author information

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Abstract

Glyphosate (N-(phosphonomethyl)glycine) is an active ingredient of the most widely used herbicide formulations in protecting agricultural and horticultural crops. Numerous results (mostly published in the years 2010-2013) concerning the action of glyphosate and its formulations in the recent decade were analyzed. Initial reports about alleged biodegradability of glyphosate in the environment turned out to be wrong. It has been shown that glyphosate remains in the soil and can reach people by spreading along with groundwater. Recent publications have shown that glyphosate is detected at low concentrations in the human blood. Publications cited in this article, which indicate a possible induction of neoplastic changes by glyphosate formulation, have raised great concern and controversy in the scientific world. Presenting adverse effects of glyphosate and its formulations we focused on the role of glyphosate formulations in hormonal disorders by impeding the expression of steroidogenic acute regulatory protein and the inhibition of aromatase activity. The impact of glyphosate on oxygen reactive species formation, changes in redox system and the effect on necrosis and apoptosis in various types of cells was shown. We also revealed that glyphosate as a phosphonate herbicide does not inhibit directly the activity of acetylcholinesterase. Based on numerous studies it was noted that commercial formulations of glyphosate exhibit higher toxicity than that of the active substance itself. The discussed problems clearly show the need to evaluate the toxicity of glyphosate and its formulations and related potential threat to humans.

http://www.ncbi.nlm.nih.gov/pubmed/24502134

“These experiments indicate glyphosate induces cell membrane stiffening, and the appearance of cytoskeleton structures at a subcellular level, for low cytotoxic concentrations whereas cells exposed to IC50 treatment exhibit control-like mechanical behavior despite obvious membrane damages.”

Glyphosate-induced stiffening of HaCaT keratinocytes, a Peak Force Tapping study on living cells.

by Heu C1, Berquand A, Elie-Caille C, Nicod L.

Abstract

The skin is the first physiological barrier, with a complex constitution, that provides defensive functions against multiple physical and chemical aggressions. Glyphosate is an extensively used herbicide that has been shown to increase the risk of cancer. Moreover there is increasing evidence suggesting that the mechanical phenotype plays an important role in malignant transformation. Atomic force microscopy (AFM) has emerged within the last decade as a powerful tool for providing a nanometer-scale resolution imaging of biological samples. Peak Force Tapping (PFT) is a newly released AFM-based investigation technique allowing extraction of chemical and mechanical properties from a wide range of samples at a relatively high speed and a high resolution. The present work uses the PFT technology to investigate HaCaT keratinocytes, a human epidermal cell line, and offers an original approach to study chemically-induced changes in the cellular mechanical properties under near-physiological conditions. These experiments indicate glyphosate induces cell membrane stiffening, and the appearance of cytoskeleton structures at a subcellular level, for low cytotoxic concentrations whereas cells exposed to IC50 (inhibitory concentration 50%) treatment exhibit control-like mechanical behavior despite obvious membrane damages. Quercetin, a well-known antioxidant, reverses the glyphosate-induced mechanical phenotype:

http://www.ncbi.nlm.nih.gov/pubmed/22369932

“Since we found genotoxic effects after short exposure to concentrations that correspond to a 450-fold dilution of spraying used in agriculture, our findings indicate that inhalation may cause DNA damage in exposed individuals”

Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells.

by Koller VJ, Fürhacker M, Nersesyan A, Mišík M, Eisenbauer M, Knasmueller S.

Abstract

Glyphosate (G) is the largest selling herbicide worldwide; the most common formulations (Roundup, R) contain poly-oxyethyleneamine as main surfactant. Recent findings indicate that G exposure may cause DNA damage and cancer in humans. Aim of this investigation was to study the cytotoxic and genotoxic properties of G and R (UltraMax) in a buccal epithelial cell line (TR146), as workers are exposed via inhalation to the herbicide. R induced acute cytotoxic effects at concentrations > 40 mg/l after 20 min, which were due to membrane damage and impairment of mitochondrial functions. With G, increased release of extracellular lactate dehydrogenase indicative for membrane damage was observed at doses > 80 mg/l. Both G and R induced DNA migration in single-cell gel electrophoresis assays at doses > 20 mg/l. Furthermore, an increase of nuclear aberrations that reflect DNA damage was observed. The frequencies of micronuclei and nuclear buds were elevated after 20-min exposure to 10-20 mg/l, while nucleoplasmatic bridges were only enhanced by R at the highest dose (20 mg/l). R was under all conditions more active than its active principle (G). Comparisons with results of earlier studies with lymphocytes and cells from internal organs indicate that epithelial cells are more susceptible to the cytotoxic and DNA-damaging properties of the herbicide and its formulation. Since we found genotoxic effects after short exposure to concentrations that correspond to a 450-fold dilution of spraying used in agriculture, our findings indicate that inhalation may cause DNA damage in exposed individuals:

http://www.ncbi.nlm.nih.gov/pubmed/22331240

“AMPA is the major environmental breakdown product of glyphosate.
AMPA was genotoxic in the three performed tests.
Very scarce data are available about AMPA potential genotoxicity.”

Genotoxicity of AMPA, the environmental metabolite of glyphosate, assessed by the Comet assay and cytogenetic tests.

by Mañas F1, Peralta L, Raviolo J, García Ovando H, Weyers A, Ugnia L, Gonzalez Cid M, Larripa I, Gorla N.

Author information

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Abstract

Formulations containing glyphosate are the most widely used herbicides in the world. AMPA is the major environmental breakdown product of glyphosate. The purpose of this study is to evaluate the in vitro genotoxicity of AMPA using the Comet assay in Hep-2 cells after 4h of incubation and the chromosome aberration (CA) test in human lymphocytes after 48h of exposition. Potential in vivo genotoxicity was evaluated through the micronucleus test in mice. In the Comet assay, the level of DNA damage in exposed cells at 2.5-7.5mM showed a significant increase compared with the control group. In human lymphocytes we found statistically significant clastogenic effect AMPA at 1.8mM compared with the control group. In vivo, the micronucleus test rendered significant statistical increases at 200-400mg/kg. AMPA was genotoxic in the three performed tests. Very scarce data are available about AMPA potential genotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/19013644

“These results indicate that the AChE-a neurotoxicity biomarker in C. decemmaculatus may be affected by exposure to environmentally relevant concentrations of glyphosate”

Glyphosate As An Acetylcholinesterase Inhibitor in Cnesterodon Decemmaculatus.

by Menéndez-Helman RJ1, Ferreyroa GV, dos Santos Afonso M, Salibián A.

Author information

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Abstract

The toxic effect of sublethal concentrations (1, 17.5 and 35 mg L(-1)) of pure glyphosate was evaluated on acetylcholinesterase (AChE) activity in the fish species, Cnesterodon decemmaculatus. Acute bioassays (96 h) under laboratory conditions were conducted and homogenates for each specimen corresponding to the anterior, middle and posterior body sections were performed. Fish survival was 100%, even at the highest concentration tested (35 mg L(-1)), in accordance with the low lethal toxicity reported for glyphosate. However, a significant inhibitory effect on AChE activity was recorded even for the lowest herbicide concentration tested (1 mg L(-1)), in the homogenates corresponding to the anterior body section. The inhibition ranged from 23 to 36%. The analytical determination of glyphosate in assay media by ion chromatography, was used to verify its stability. These results indicate that AChE-a neurotoxicity biomarker-in C. decemmaculatus may be affected by exposure to environmentally relevant concentrations of glyphosate:

http://www.ncbi.nlm.nih.gov/pubmed/22002176

“In conclusion, glyphosate causes dysbiosis which favors the production of BoNT in the rumen. The global regulations restrictions for the use of glyphosate should be re-evaluated”

The influence of glyphosate on the microbiota and production of botulinum neurotoxin during ruminal fermentation

by Ackermann W1, Coenen M, Schrödl W, Shehata AA, Krüger M.

Author information

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Abstract

The aim of the present study is to investigate the impact of glyphosate on the microbiota and on the botulinum neurotoxin (BoNT) expression during in vitro ruminal fermentation. This study was conducted using two DAISY(II)-incubators with four ventilated incubation vessels filled with rumen fluid of a 4-year-old non-lactating Holstein-Friesian cow. Two hundred milliliter rumen fluid and 800 ml buffer solution were used with six filter bags containing 500 mg concentrated feed or crude fiber-enriched diet. Final concentrations of 0, 1, 10, and 100 µg/ml of glyphosate in the diluted rumen fluids were added and incubated under CO2-aerated conditions for 48 h. The protozoal population was analyzed microscopically and the ruminal flora was characterized using the fluorescence in situ hybridization technique. Clostridium botulinum and BoNT were quantified using most probable number and ELISA, respectively. Results showed that glyphosate had an inhibitory effect on select groups of the ruminal microbiota, but increased the population of pathogenic species. The BoNT was produced during incubation when inoculum was treated with high doses of glyphosate. In conclusion, glyphosate causes dysbiosis which favors the production of BoNT in the rumen. The global regulations restrictions for the use of glyphosate should be re-evaluated:

http://www.ncbi.nlm.nih.gov/pubmed/25407376

“Pesticides are the main environmental factor associated with the etiology of human neurodegenerative disorders such as Parkinson’s disease. Thus, these results may contribute to understand the effect(s) of chronic and simultaneous exposure to pesticides on cell survival.”

Effect of pesticides on cell survival in liver and brain rat tissues

Author information

by Astiz M1,
de Alaniz MJ, Marra CA.
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Abstract

Pesticides are the main environmental factor associated with the etiology of human neurodegenerative disorders such as Parkinson’s disease. Our laboratory has previously demonstrated that the treatment of rats with low doses of dimethoate, zineb or glyphosate alone or in combination induces oxidative stress (OS) in liver and brain. The aim of the present work was to investigate if the pesticide-induced OS was able to affect brain and liver cell survival. The treatment of Wistar rats with the pesticides (i.p. 1/250 LD50, three times a week for 5 weeks) caused loss of mitochondrial transmembrane potential and cardiolipin content, especially in substantia nigra (SN), with a concomitant increase of fatty acid peroxidation. The activation of calpain apoptotic cascade (instead of the caspase-dependent pathway) would be responsible for the DNA fragmentation pattern observed. Thus, these results may contribute to understand the effect(s) of chronic and simultaneous exposure to pesticides on cell survival:

http://www.ncbi.nlm.nih.gov/pubmed/19493570

“Herbicides have been recognized as the main environmental factor associated with human neurodegenerative disorders such as Parkinson’s disease. Furthermore, the results showed that glyphosate induced cell death via autophagy pathways in addition to activating apoptotic pathways of cellular death.”

Glyphosate induced cell death through apoptotic and autophagic mechanisms

by Gui YX1, Fan XN, Wang HM, Wang G, Chen SD.

Author information

1Department of Neurology & Institute of Neurology, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China.

Abstract

Herbicides have been recognized as the main environmental factor associated with human neurodegenerative disorders such as Parkinson’s disease (PD). Previous studies indicated that the exposure to glyphosate, a widely used herbicide, is possibly linked to Parkinsonism, however the underlying mechanism remains unclear. We investigated the neurotoxic effects of glyphosate in differentiated PC12 cells and discovered that it inhibited viability of differentiated PC12 cells in dose-and time-dependent manners. Furthermore, the results showed that glyphosate induced cell death via autophagy pathways in addition to activating apoptotic pathways. Interestingly, deactivation of Beclin-1 gene attenuated both apoptosis and autophagy in glyphosate treated differentiated PC12 cells, suggesting that Beclin-1 gene is involved in the crosstalk between the two mechanisms:

http://www.ncbi.nlm.nih.gov/pubmed/22504123

Parkinsonism after glycine-derivate [Glyphosate] exposure

by Barbosa ER1, Leiros da Costa MD, Bacheschi LA, Scaff M, Leite CC.

Author information

1Divisão de Clínica Neurológica, Hospital das Clínicas da Faculdade, Medicina da Universidade, São Paulo, São Paulo, Brazil.

Abstract

This 54-year-old man accidentally sprayed himself with the chemical agent glyphosate, a herbicide derived from the amino acid glycine. He developed disseminated skin lesions 6 hours after the accident. One month later, he developed a symmetrical parkinsonian syndrome. Two years after the initial exposure to glyphosate, magnetic resonance imaging revealed hyperintense signal in the globus pallidus and substantia nigra, bilaterally, on T2-weighted images. Levodopa/benserazide 500/125 mg daily provided satisfactory clinical outcome:

http://www.ncbi.nlm.nih.gov/pubmed/11391760

“The results of this study; unexpected early deaths, large female mammary tumors, disabled pituitary glands, liver necrosis, severe kidney nephropathies and chronic kidney deficiencies are all explained by Roundup™ poisoning”

Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize

by Séralini GE1, Clair E, Mesnage R, Gress S,
Defarge N, Malatesta M, Hennequin D, de Vendômois JS

Author information

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Abstract

The health effects of a Roundup-tolerant genetically modified maize (from 11% in the diet), cultivated with or without Roundup, and Roundup alone (from 0.1 ppb in water), were studied 2 years in rats. In females, all treated groups died 2-3 times more than controls, and more rapidly. This difference was visible in 3 male groups fed GMOs. All results were hormone and sex dependent, and the pathological profiles were comparable. Females developed large mammary tumors almost always more often than and before controls, the pituitary was the second most disabled organ; the sex hormonal balance was modified by GMO and Roundup treatments. In treated males, liver congestions and necrosis were 2.5-5.5 times higher. This pathology was confirmed by optic and transmission electron microscopy. Marked and severe kidney nephropathies were also generally 1.3-2.3 greater. Males presented 4 times more large palpable tumors than controls which occurred up to 600 days earlier. Biochemistry data confirmed very significant kidney chronic deficiencies; for all treatments and both sexes, 76% of the altered parameters were kidney related. These results can be explained by the non linear endocrine-disrupting effects of Roundup, but also by the overexpression of the transgene in the GMO and its metabolic consequences:

http://www.ncbi.nlm.nih.gov/pubmed/22999595

“This work clearly confirms that the adjuvants in Roundup formulations are not inert. Moreover, the proprietary mixtures available on the market could cause cell damage and even death around residual levels to be expected, especially in food derived from Roundup formulation-treated crops.”

Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells

by Benachour N1, Séralini GE

Author information

1UniVersity of Caen
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Abstract

We have evaluated the toxicity of four glyphosate (G)-based herbicides in Roundup formulations, from 10(5) times dilutions, on three different human cell types. This dilution level is far below agricultural recommendations and corresponds to low levels of residues in food or feed. The formulations have been compared to G alone and with its main metabolite AMPA or with one known adjuvant of R formulations, POEA. HUVEC primary neonate umbilical cord vein cells have been tested with 293 embryonic kidney and JEG3 placental cell lines. All R formulations cause total cell death within 24 h, through an inhibition of the mitochondrial succinate dehydrogenase activity, and necrosis, by release of cytosolic adenylate kinase measuring membrane damage. They also induce apoptosis via activation of enzymatic caspases 3/7 activity. This is confirmed by characteristic DNA fragmentation, nuclear shrinkage (pyknosis), and nuclear fragmentation (karyorrhexis), which is demonstrated by DAPI in apoptotic round cells. G provokes only apoptosis, and HUVEC are 100 times more sensitive overall at this level. The deleterious effects are not proportional to G concentrations but rather depend on the nature of the adjuvants. AMPA and POEA separately and synergistically damage cell membranes like R but at different concentrations. Their mixtures are generally even more harmful with G. In conclusion, the R adjuvants like POEA change human cell permeability and amplify toxicity induced already by G, through apoptosis and necrosis. The real threshold of G toxicity must take into account the presence of adjuvants but also G metabolism and time-amplified effects or bioaccumulation. This should be discussed when analyzing the in vivo toxic actions of R. This work clearly confirms that the adjuvants in Roundup formulations are not inert. Moreover, the proprietary mixtures available on the market could cause cell damage and even death around residual levels to be expected, especially in food and feed derived from R formulation-treated crops:

http://www.ncbi.nlm.nih.gov/pubmed/19105591

“The cytotoxic, and potentially endocrine-disrupting effects of Roundup are thus amplified with time. Taken together, these data suggest that Roundup exposure may affect human reproduction and fetal development in case of even low dose contamination”

Time- and dose-dependent effects of roundup on human embryonic and placental cells

by Benachour N1, Sipahutar H, Moslemi S,
Gasnier C, Travert C, Séralini GE.

Author information

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Abstract

Roundup is the major herbicide used worldwide, in particular on genetically modified plants that have been designed to tolerate it. We have tested the toxicity and endocrine disruption potential of Roundup (Bioforce on human embryonic 293 and placental-derived JEG3 cells, but also on normal human placenta and equine testis. The cell lines have proven to be suitable to estimate hormonal activity and toxicity of pollutants. The median lethal dose (LD(50)) of Roundup with embryonic cells is 0.3% within 1 h in serum-free medium, and it decreases to reach 0.06% (containing among other compounds 1.27 mM glyphosate) after 72 h in the presence of serum. In these conditions, the embryonic cells appear to be 2-4 times more sensitive than the placental ones. In all instances, Roundup (generally used in agriculture at 1-2%, i.e., with 21-42 mM glyphosate) is more efficient than its active ingredient, glyphosate, suggesting a synergistic effect provoked by the adjuvants present in Roundup. We demonstrated that serum-free cultures, even on a short-term basis (1 h), reveal the xenobiotic impacts that are visible 1-2 days later in serum. We also document at lower non-overtly toxic doses, from 0.01% (with 210 microM glyphosate) in 24 h, that Roundup is an aromatase disruptor. The direct inhibition is temperature-dependent and is confirmed in different tissues and species (cell lines from placenta or embryonic kidney, equine testicular, or human fresh placental extracts). Furthermore, glyphosate acts directly as a partial inactivator on microsomal aromatase, independently of its acidity, and in a dose-dependent manner. The cytotoxic, and potentially endocrine-disrupting effects of Roundup are thus amplified with time. Taken together, these data suggest that Roundup exposure may affect human reproduction and fetal development in case of contamination. Chemical mixtures in formulations appear to be underestimated regarding their toxic or hormonal impact:

http://www.ncbi.nlm.nih.gov/pubmed/17486286

“Previous studies demonstrate that glyphosate exposure is associated with oxidative damage and neurotoxicity.”

Mechanisms underlying the neurotoxicity induced by glyphosate-based herbicide in immature rat hippocampus: involvement of glutamate excitotoxicity

by Cattani D1, de Liz Oliveira Cavalli VL1, Heinz Rieg CE1, Domingues JT1, Dal-Cim T1, Tasca CI1, Mena Barreto Silva FR1, Zamoner A2.

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Abstract

Previous studies demonstrate that glyphosate exposure is associated with oxidative damage and neurotoxicity. Therefore, the mechanism of glyphosate-induced neurotoxic effects needs to be determined. The aim of this study was to investigate whether Roundup(®) (a glyphosate-based herbicide) leads to neurotoxicity in hippocampus of immature rats following acute (30min) and chronic (pregnancy and lactation) pesticide exposure. Maternal exposure to pesticide was undertaken by treating dams orally with 1% Roundup(®) (0.38% glyphosate) during pregnancy and lactation (till 15-day-old). Hippocampal slices from 15 day old rats were acutely exposed to Roundup(®) (0.00005-0.1%) during 30min and experiments were carried out to determine whether glyphosate affects (45)Ca(2+) influx and cell viability. Moreover, we investigated the pesticide effects on oxidative stress parameters, (14)C-å-methyl-amino-isobutyric acid ((14)C-MeAIB) accumulation, as well as glutamate uptake, release and metabolism. Results showed that acute exposure to Roundup(®) (30min) increases (45)Ca(2+) influx by activating NMDA receptors and voltage-dependent Ca(2+) channels, leading to oxidative stress and neural cell death. The mechanisms underlying Roundup(®)-induced neurotoxicity also involve the activation of CaMKII and ERK. Moreover, acute exposure to Roundup(®) increased (3)H-glutamate released into the synaptic cleft, decreased GSH content and increased the lipoperoxidation, characterizing excitotoxicity and oxidative damage. We also observed that both acute and chronic exposure to Roundup(®) decreased (3)H-glutamate uptake and metabolism, while induced (45)Ca(2+) uptake and (14)C-MeAIB accumulation in immature rat hippocampus. Taken together, these results demonstrated that Roundup(®) might lead to excessive extracellular glutamate levels and consequently to glutamate excitotoxicity and oxidative stress in rat hippocampus:

http://www.ncbi.nlm.nih.gov/pubmed/24636977

“The herbicide glyphosate causes behavioral changes and neurological disorders”

The herbicide glyphosate causes behavioral changes and alterations in dopaminergic markers in male Sprague-Dawley rat

by Hernández-Plata I1, Giordano M1, Díaz-Muñoz M2, Rodríguez VM3.

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Abstract

Glyphosate (Glyph) is the active ingredient of several herbicide formulations. Reports of Glyph exposure in humans and animal models suggest that it may be neurotoxic. To evaluate the effects of Glyph on the nervous system, male Sprague-Dawley rats were given six intraperitoneal injections of 50, 100, or 150mg Glyph/kg BW over 2 weeks (three injections/week). We assessed dopaminergic markers and their association with locomotor activity. Repeated exposure to Glyph caused hypoactivity immediately after each injection, and it was also apparent 2 days after the last injection in rats exposed to the highest dose. Glyph did not decrease monoamines, tyrosine hydroxylase (TH), or mesencephalic TH+ cells when measured 2 or 16 days after the last Glyph injection. In contrast, Glyph decreased specific binding to D1 dopamine (DA) receptors in the nucleus accumbens (NAcc) when measured 2 days after the last Glyph injection. Microdialysis experiments showed that a systemic injection of 150mg Glyph/kg BW decreased basal extracellular DA levels and high-potassium-induced DA release in striatum. Glyph did not affect the extracellular concentrations of 3,4-dihydroxyphenylacetic acid or homovanillic acid. These results indicate that repeated Glyph exposure results in hypoactivity accompanied by decreases in specific binding to D1-DA receptors in the NAcc, and that acute exposure to Glyph has evident effects on striatal DA levels. Additional experiments are necessary in order to unveil the specific targets of Glyph on dopaminergic system, and whether Glyph could be affecting other neurotransmitter systems involved in motor control:

http://www.ncbi.nlm.nih.gov/pubmed/25522657

“We have evaluated the toxicity of four glyphosate (G)-based herbicides in Roundup formulations, from 10(5) times dilutions, on three different human cell types. This dilution level is far below agricultural recommendations and corresponds to low levels of residues in food or feed. This work clearly confirms that the adjuvants in Roundup formulations are not inert. Moreover, the proprietary mixtures available on the market could cause cell damage and even death around residual levels to be expected, especially in food and feed derived from R formulation-treated crops.”

Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells

by Benachour N1, Séralini GE

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Abstract

We have evaluated the toxicity of four glyphosate (G)-based herbicides in Roundup formulations, from 10(5) times dilutions, on three different human cell types. This dilution level is far below agricultural recommendations and corresponds to low levels of residues in food or feed. The formulations have been compared to G alone and with its main metabolite AMPA or with one known adjuvant of R formulations, POEA. HUVEC primary neonate umbilical cord vein cells have been tested with 293 embryonic kidney and JEG3 placental cell lines. All R formulations cause total cell death within 24 h, through an inhibition of the mitochondrial succinate dehydrogenase activity, and necrosis, by release of cytosolic adenylate kinase measuring membrane damage. They also induce apoptosis via activation of enzymatic caspases 3/7 activity. This is confirmed by characteristic DNA fragmentation, nuclear shrinkage (pyknosis), and nuclear fragmentation (karyorrhexis), which is demonstrated by DAPI in apoptotic round cells. G provokes only apoptosis, and HUVEC are 100 times more sensitive overall at this level. The deleterious effects are not proportional to G concentrations but rather depend on the nature of the adjuvants. AMPA and POEA separately and synergistically damage cell membranes like R but at different concentrations. Their mixtures are generally even more harmful with G. In conclusion, the R adjuvants like POEA change human cell permeability and amplify toxicity induced already by G, through apoptosis and necrosis. The real threshold of G toxicity must take into account the presence of adjuvants but also G metabolism and time-amplified effects or bioaccumulation. This should be discussed when analyzing the in vivo toxic actions of R. This work clearly confirms that the adjuvants in Roundup formulations are not inert. Moreover, the proprietary mixtures available on the market could cause cell damage and even death around residual levels to be expected, especially in food and feed derived from R formulation-treated crops:

http://www.ncbi.nlm.nih.gov/pubmed/19105591

“Many neurological diseases, including autism, depression, dementia, anxiety disorder and Parkinson’s disease, are associated with abnormal sleep patterns, which are directly linked to pineal gland dysfunction. The pineal gland is highly susceptible to environmental toxicants. Two pervasive substances in modern industrialized nations are aluminum and glyphosate, the active ingredient in the herbicide, Roundup®. In this paper, we show how these two toxicants work synergistically to induce neurological damage.”

Aluminum and Glyphosate Can Synergistically Induce Pineal Gland Pathology: Connection to Gut Dysbiosis and Neurological Disease

by Stephanie Seneff1*, Nancy Swanson2, Chen Li1

1Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA, USA
2Independent Researcher, Abacus Enterprises, Lummi Island, WA, USA
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Abstract

Many neurological diseases, including autism, depression, dementia, anxiety disorder and Parkinson’s disease, are associated with abnormal sleep patterns, which are directly linked to pineal gland dysfunction. The pineal gland is highly susceptible to environmental toxicants. Two pervasive substances in modern industrialized nations are aluminum and glyphosate, the active ingredient in the herbicide, Roundup®. In this paper, we show how these two toxicants work synergistically to induce neurological damage. Glyphosate disrupts gut bacteria, leading to an overgrowth of Clostridium difficile. Its toxic product, p-cresol, is linked to autism in both human and mouse models. p-Cresol enhances uptake of aluminum via transferrin. Anemia, a result of both aluminum disruption of heme and impaired heme synthesis by glyphosate, leads to hypoxia, which induces increased pineal gland transferrin synthesis. Premature birth is associated with hypoxic stress and with substantial increased risk to the subsequent development of autism, linking hypoxia to autism. Glyphosate chelates aluminum, allowing ingested aluminum to bypass the gut barrier. This leads to anemia-induced hypoxia, promoting neurotoxicity and damaging the pineal gland. Both glyphosate and aluminum disrupt cytochrome P450 enzymes, which are involved in melatonin metabolism. Furthermore, melatonin is derived from tryptophan, whose synthesis in plants and microbes is blocked by glyphosate. We also demonstrate a plausible role for vitamin D3 dysbiosis in impaired gut function and impaired serotonin synthesis. This paper proposes that impaired sulfate supply to the brain mediates the damage induced by the synergistic action of aluminum and glyphosate on the pineal gland and related midbrain nuclei.

www.scirp.org/journal/Paperinformation.aspx?PaperID=53106

“Chronically ill humans had significantly higher glyphosate residues in urine than healthy humans.”

Detection of Glyphosate Residues in Animals and Humans

Environmental & Analytical Toxicology

by Monika Krüger1, Philipp Schledorn1, Wieland Schrödl1, Hans-Wolfgang Hoppe2,
Walburga Lutz3 and Awad A. Shehata1,4*

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3Wildlife Research Institute, Bonn, Germany
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Abstract

In the present study glyphosate residues were tested in urine and different organs of dairy cows as well as in urine of hares, rabbits and humans using ELISA and Gas Chromatography-Mass Spectroscopy (GC-MS). The correlation coefficients between ELISA and GC-MS were 0.96, 0.87, 0.97and 0.96 for cattle, human, and rabbit urine and organs, respectively. The recovery rate of glyphosate in spiked meat using ELISA was 91%. Glyphosate excretion in German dairy cows was significantly lower than Danish cows. Cows kept in genetically modified free area had significantly lower glyphosate concentrations in urine than conventional husbandry cows. Also glyphosate was detected in different organs of slaughtered cows as intestine, liver, muscles, spleen and kidney. Fattening rabbits showed significantly higher glyphosate residues in urine than hares. Moreover, glyphosate was significantly higher in urine of humans with conventional feeding. Furthermore, chronically ill humans showed significantly higher glyphosate residues in urine than healthy population. The presence of glyphosate residues in both humans and animals could haul the entire population towards numerous health hazards, studying the impact of glyphosate residues on health is warranted and the global regulations for the use of glyphosate may have to be re-evaluated.

Conclusions

Glyphosate residue could reach humans and animals through feed and excreted in urine. Presence of glyphosate in urine and its accumulation in animal tissues is alarming even at low concentrations. Unknown impacts of glyphosate on human and animal health warrants further investigations of glyphosate residues in vertebrates and other non-target organisms. Chronically ill humans had significantly higher glyphosate residues in urine than healthy humans.

Full text, graphs, charts and 30 references

http://www.omicsonline.org/open-access/detection-of-glyphosate-residues-in-animals-and-humans-2161-0525.1000210.pdf

“It is speculated that genetically modified food (GMF)/genetically modified organism (GMO) is responsible for infertility development”

Hypothetical link between infertility and genetically modified food

by Gao M, Li B, Yuan W, Zhao L, Zhang X1.

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Abstract

It is speculated that genetically modified food (GMF)/genetically modified organism (GMO) is responsible for infertility development. The risk linked with a wide use of GMFs/GMOs offers the basic elements for social criticism. However, to date, it has not been justified whether the bad effects are directly resulted from products of genetic modifications or trans-genesis process. Extensive experience with the risk assessment of whole foods has been applied recently on the safety and nutritional testing of GMFs/GMOs. Investigations have tested the safety of GMFs including sub-acute, chronic, reproductive, multi-generation and carcinogenicity studies. We extrapolated the potential risks associated with GMFs/GMOs on reproduction, and analyzed the multi-aspect linked between infertility and GMFs/GMOs. It could be conjectured that GMFs/GMOs could be potential hazard on reproduction, linking to the development of infertility through influencing the endocrine metabolism, endometriosis. However, little evidence shows the impaction on embryo or reproductive related tumor due to the limited literatures, and needs further research. The article presents some related patents on GMFs/GMOs, and some methods for tracking GMOs.

http://www.ncbi.nlm.nih.gov/pubmed/25342149

“it can be reckless to continue following expert opinion when a preponderance of evidence is amassed that conflicts with this opinion”

Expert opinion vs. empirical evidence: the precautionary principle applied to GM crops.

by Herman RA1, Raybould A2.

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Abstract

Expert opinion is often sought by government regulatory agencies when there is insufficient empirical evidence to judge the safety implications of a course of action. However, it can be reckless to continue following expert opinion when a preponderance of evidence is amassed that conflicts with this opinion. Factual evidence should always trump opinion in prioritizing the information that is used to guide regulatory policy. Evidence-based medicine has seen a dramatic upturn in recent years spurred by examples where evidence indicated that certain treatments recommended by expert opinions increased death rates. We suggest that scientific evidence should also take priority over expert opinion in the regulation of genetically modified crops (GM). Examples of regulatory data requirements that are not justified based on the mass of evidence are described, and it is suggested that expertise in risk assessment should guide evidence-based regulation of GM crops.

http://www.ncbi.nlm.nih.gov/pubmed/24637724

“The most detailed regulatory tests on the GMOs are three-month long feeding trials of laboratory rats, which are biochemically assessed. The tests are not compulsory, and are not independently conducted. The test data and the corresponding results are kept in secret by the companies.”

Debate on GMOs health risks after statistical findings in regulatory tests

by de Vendômois JS1, Cellier D, Vélot C,
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Abstract

We summarize the major points of international debate on health risk studies for the main commercialized edible GMOs. These GMOs are soy, maize and oilseed rape designed to contain new pesticide residues since they have been modified to be herbicide-tolerant (mostly to Roundup) or to produce mutated Bt toxins. The debated alimentary chronic risks may come from unpredictable insertional mutagenesis effects, metabolic effects, or from the new pesticide residues. The most detailed regulatory tests on the GMOs are three-month long feeding trials of laboratory rats, which are biochemically assessed. The tests are not compulsory, and are not independently conducted. The test data and the corresponding results are kept in secret by the companies. Our previous analyses of regulatory raw data at these levels, taking the representative examples of three GM maize NK 603, MON 810, and MON 863 led us to conclude that hepatorenal toxicities were possible, and that longer testing was necessary. Our study was criticized by the company developing the GMOs in question and the regulatory bodies, mainly on the divergent biological interpretations of statistically significant biochemical and physiological effects. We present the scientific reasons for the crucially different biological interpretations and also highlight the shortcomings in the experimental protocols designed by the company. The debate implies an enormous responsibility towards public health and is essential due to nonexistent traceability or epidemiological studies in the GMO-producing countries:

http://www.ncbi.nlm.nih.gov/pubmed/20941377

“All chemicals induced significant numbers of mutations in at least one of the cell types tested”

Mutagenicity testing of nine herbicides and pesticides currently used in agriculture

by Kale PG1, Petty BT Jr, Walker S, Ford JB, Dehkordi N, Tarasia S, Tasie BO, Kale R, Sohni YR.

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Abstract

Nine herbicides and pesticides were tested for their mutagenicity using the Drosophila sex-linked recessive lethal mutation assay. These are Ambush, Treflan, Blazer, Roundup, 2,4-D Amine, Crossbow, Galecron, Pramitol, and Pondmaster. All of these are in wide use at present. Unlike adult feeding and injection assays, the larvae were allowed to grow in medium with the test chemical, thereby providing long and chronic exposure to the sensitive and dividing diploid cells, i.e., mitotically active spermatogonia and sensitive spermatocytes. All chemicals induced significant numbers of mutations in at least one of the cell types tested. Some of these compounds were found to be negative in earlier studies. An explanation for the difference in results is provided. It is probable that different germ cell stages and treatment regimens are suitable for different types of chemicals. larval treatment may still be valuable and can complement adult treatment in environmental mutagen testing:

http://www.ncbi.nlm.nih.gov/pubmed/7698107

“We also observed an early onset of puberty but no effect on the body growth in these animals. These results suggest that maternal exposure to glyphosate disturbed the masculinization process and promoted behavioral changes and histological and endocrine problems in reproductive parameters.”

Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression

by Romano MA1, Romano RM, Santos LD, Wisniewski P, Campos DA, de Souza PB, Viau P, Bernardi MM, Nunes MT, de Oliveira CA.

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Abstract

Sexual differentiation in the brain takes place from late gestation to the early postnatal days. This is dependent on the conversion of circulating testosterone into estradiol by the enzyme aromatase. The glyphosate was shown to alter aromatase activity and decrease serum testosterone concentrations. Thus, the aim of this study was to investigate the effect of gestational maternal glyphosate exposure (50 mg/kg, NOAEL for reproductive toxicity) on the reproductive development of male offspring. Sixty-day-old male rat offspring were evaluated for sexual behavior and partner preference; serum testosterone concentrations, estradiol, FSH and LH; the mRNA and protein content of LH and FSH; sperm production and the morphology of the seminiferous epithelium; and the weight of the testes, epididymis and seminal vesicles. The growth, the weight and age at puberty of the animals were also recorded to evaluate the effect of the treatment. The most important findings were increases in sexual partner preference scores and the latency time to the first mount; testosterone and estradiol serum concentrations; the mRNA expression and protein content in the pituitary gland and the serum concentration of LH; sperm production and reserves; and the height of the germinal epithelium of seminiferous tubules. We also observed an early onset of puberty but no effect on the body growth in these animals. These results suggest that maternal exposure to glyphosate disturbed the masculinization process and promoted behavioral changes and histological and endocrine problems in reproductive parameters. These changes associated with the hypersecretion of androgens increased gonadal activity and sperm production.

http://www.ncbi.nlm.nih.gov/pubmed/22120950

“Here we show that glyphosate is toxic to human placental JEG3 cells within 18 hours with concentrations lower than those found with agricultural use, and this effect increases with concentration and time or in the presence of Roundup adjuvants. Surprisingly, Roundup is always more toxic than its active ingredient. We conclude that endocrine and toxic effects of Roundup, not just glyphosate, can be observed in mammals. We suggest that the presence of Roundup adjuvants enhances glyphosate bioavailability and/or bioaccumulation.”

Differential effects of glyphosate and roundup on human placental cells and aromatase

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Abstract

Roundup is a glyphosate-based herbicide used worldwide, including on most genetically modified plants that have been designed to tolerate it. Its residues may thus enter the food chain, and glyphosate is found as a contaminant in rivers. Some agricultural workers using glyphosate have pregnancy problems, but its mechanism of action in mammals is questioned. Here we show that glyphosate is toxic to human placental JEG3 cells within 18 hr with concentrations lower than those found with agricultural use, and this effect increases with concentration and time or in the presence of Roundup adjuvants. Surprisingly, Roundup is always more toxic than its active ingredient. We tested the effects of glyphosate and Roundup at lower nontoxic concentrations on aromatase, the enzyme responsible for estrogen synthesis. The glyphosate-based herbicide disrupts aromatase activity and mRNA levels and interacts with the active site of the purified enzyme, but the effects of glyphosate are facilitated by the Roundup formulation in microsomes or in cell culture. We conclude that endocrine and toxic effects of Roundup, not just glyphosate, can be observed in mammals. We suggest that the presence of Roundup adjuvants enhances glyphosate bioavailability and/or bioaccumulation.

Full text, graphs, charts and 38 references

http://stopogm.net/sites/stopogm.net/files/webfm/plataforma/DifferentialEffectsGlyphosate.pdf

“We may conclude that glyphosate-Roundup is toxic to the dams and induces developmental retardation of the fetal skeleton.”

The teratogenic potential of the herbicide glyphosate-Roundup in Wistar rats

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Abstract

The aim of this study was to assess the teratogenicity of the herbicide glyphosate-Roundup (as commercialized in Brazil) to Wistar rats. Dams were treated orally with water or 500, 750 or 1000 mg/kg glyphosate from day 6 to 15 of pregnancy. Cesarean sections were performed on day 21 of pregnancy, and number of corpora lutea, implantation sites, living and dead fetuses, and resorptions were recorded. Weight and gender of the fetuses were determined, and fetuses were examined for external malformations and skeletal alterations. The organs of the dams were removed and weighed. Results showed a 50%, mortality rate for dams treated with 1000 mg/kg glyphosate. Skeletal alterations were observed in 15.4, 33.1, 42.0 and 57.3% of fetuses from the control, 500, 750 and 1000 mg/kg glyphosate groups, respectively. We may conclude that glyphosate-Roundup is toxic to the dams and induces developmental retardation of the fetal skeleton.

http://www.ncbi.nlm.nih.gov/pubmed/12765238

“We show that from 1 to 48 hours of Roundup exposure Leydig cells are damaged. Within 24-48 hours this formulation is also toxic on other cells, mainly by necrosis, by contrast to glyphosate alone which is essentially toxic on Sertoli cells. Later, it also induces apoptosis at higher doses in germ cells and in Sertoli/germ cells co-cultures. At lower non toxic concentrations of Roundup and glyphosate (1ppm), the main endocrine disruption is a testosterone decrease by 35%”

A glyphosate-based herbicide induces necrosis and apoptosis in mature rat testicular cells in vitro and testosterone decrease at lower levels

by Clair E1, Mesnage R, Travert C, Séralini GÉ.

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Abstract

The major herbicide used worldwide, Roundup, is a glyphosate-based pesticide with adjuvants. Glyphosate, its active ingredient in plants and its main metabolite (AMPA) are among the first contaminants of surface waters. Roundup is being used increasingly in particular on genetically modified plants grown for food and feed that contain its residues. Here we tested glyphosate and its formulation on mature rat fresh testicular cells from 1 to 10000ppm, thus from the range in some human urine and in environment to agricultural levels. We show that from 1 to 48h of Roundup exposure Leydig cells are damaged. Within 24-48h this formulation is also toxic on the other cells, mainly by necrosis, by contrast to glyphosate alone which is essentially toxic on Sertoli cells. Later, it also induces apoptosis at higher doses in germ cells and in Sertoli/germ cells co-cultures. At lower non toxic concentrations of Roundup and glyphosate (1ppm), the main endocrine disruption is a testosterone decrease by 35%. The pesticide has thus an endocrine impact at very low environmental doses, but only a high contamination appears to provoke an acute rat testicular toxicity. This does not anticipate the chronic toxicity which is insufficiently tested, and only with glyphosate in regulatory tests.

http://www.ncbi.nlm.nih.gov/pubmed/12765238

“These results suggest that commercial formulation of glyphosate is a potent endocrine disruptor in vivo, causing disturbances in the reproductive development of rats when the exposure was performed during the puberty period”

Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology

by Romano RM1, Romano MA,
Bernardi MM, Furtado PV, Oliveira CA.

Abstract

Glyphosate is a herbicide widely used to kill weeds both in agricultural and non-agricultural landscapes. Its reproductive toxicity is related to the inhibition of a StAR protein and an aromatase enzyme, which causes an in vitro reduction in testosterone and estradiol synthesis. Studies in vivo about this herbicide effects in prepubertal Wistar rats reproductive development were not performed at this moment. Evaluations included the progression of puberty, body development, the hormonal production of testosterone, estradiol and corticosterone, and the morphology of the testis. Results showed that the herbicide (1) significantly changed the progression of puberty in a dose-dependent manner; (2) reduced the testosterone production, in semineferous tubules' morphology, decreased significantly the epithelium height ($P < 0.001$; control = 85.8 +/- 2.8 microm; 5 mg/kg = 71.9 +/- 5.3 microm; 50 mg/kg = 69.1 +/- 1.7 microm; 250 mg/kg = 65.2 +/- 1.3 microm) and increased the luminal diameter ($P < 0.01$; control = 94.0 +/- 5.7 microm; 5 mg/kg = 116.6 +/- 6.6 microm; 50 mg/kg = 114.3 +/- 3.1 microm; 250 mg/kg = 130.3 +/- 4.8 microm); (4) no difference in tubular diameter was observed; and (5) relative to the controls, no differences in serum corticosterone or estradiol levels were detected, but the concentrations of testosterone serum were lower in all treated groups ($P < 0.001$; control = 154.5 +/- 12.9 ng/dL; 5 mg/kg = 108.6 +/- 19.6 ng/dL; 50 mg/dL = 84.5 +/- 12.2 ng/dL; 250 mg/kg = 76.9 +/- 14.2 ng/dL). These results suggest that commercial formulation of glyphosate is a potent endocrine disruptor in vivo, causing disturbances in the reproductive development of rats when the exposure was performed during the puberty period:

http://www.ncbi.nlm.nih.gov/pubmed/20012598

CHAPTER ELEVEN

Parabens

The Peer Review

Propyl paraben is an endocrine-disrupting chemical used as a food preservative. It's commonly found in tortillas, muffins, and food dyes and may also contaminate foods via packaging. Research has shown that 91 percent of Americans have propyl paraben in their urine, and tests on beverages, dairy products, meat, and vegetables found the chemical in about half of the samples.

Propyl paraben has weak estrogenic activity, which makes it relevant when it comes to estrogen-sensitive cancers like breast cancer. This substance has been found to accelerate the growth of breast cancer cells, impair fertility in women, and reduce sperm counts and testosterone levels in men.

Propyl paraben is an environmental and food contaminant found almost everywhere in everything and this chemical should always be avoided.

“Furthermore, as alkyl-chain length increased, the ecotoxicity of parabens and their degradation products was found to be also increased.”

Water Research • March 2016

Theoretical investigation on the kinetics and mechanisms of hydroxyl radical-induced transformation of parabens and its consequences for toxicity: Influence of alkyl-chain length

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Abstract

As emerging organic contaminants (EOCs), the ubiquitous presence of preservative parabens in water causes a serious environmental concern. Hydroxyl radical ((•)OH) is a strong oxidant that can degrade EOCs through photochemistry in surface water environments as well as in advanced oxidation processes (AOPs). To better understand the degradation mechanisms, kinetics, and products toxicity of the preservative parabens in aquatic environments and AOPs, the (•)OH-initiated degradation reactions of the four parabens were investigated systematically using a computational approach. The four studied parabens with increase of alkyl-chain length were methylparaben (MPB), ethylparaben (EPB), propylparaben (PPB), and dibutylparaben (BPB). Results showed that the four parabens can be initially attacked by (•)OH through (•)OH-addition and H-abstraction routes. The (•)OH-addition route was more important for the degradation of shorter alkyl-chain parabens like MPB and EPB, while the H-abstraction route was predominant for the degradation of parabens with longer alkyl-chain for example PPB and BPB. In assessing the aquatic toxicity of parabens and their degradation products using the model calculations, the products of the (•)OH-addition route were found to be more toxic to green algae than original parabens. Although all degradation products were less toxic to daphnia and fish than corresponding parental parabens, they could be still harmful to these aquatic organisms. Furthermore, as alkyl-chain length increased, the ecotoxicity of parabens and their degradation products was found to be also increased.

http://www.ncbi.nlm.nih.gov/pubmed/26773489

Water Research • January 2015

Occurrence, fate and behavior of parabens in aquatic environments: a review

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Abstract

Parabens are esters of para-hydroxybenzoic acid, with an alkyl (methyl, ethyl, propyl, butyl or heptyl) or benzyl group. They are mainly used as preservatives in foodstuffs, cosmetics and pharmaceutical drugs. Parabens may act as weak endocrine disrupter chemicals, but controversy still surrounds the health effects of these compounds. Despite being used since the mid-1920s, it was only in 1996 that the first analytical results of their occurrence in water were published. Considered as emerging contaminants, it is useful to review the knowledge acquired over the last decade regarding their occurrence, fate and behavior in aquatic environments. Despite treatments that eliminate them relatively well from wastewater, parabens are always present at low concentration levels in effluents of wastewater treatment plants. Although they are biodegradable, they are ubiquitous in surface water and sediments, due to consumption of paraben-based products and continuous introduction into the environment. Methylparaben and propylparaben predominate, reflecting the composition of paraben mixtures in common consumer products. Being compounds containing phenolic hydroxyl groups, parabens can react readily with free chlorine, yielding halogenated by-products. Chlorinated parabens have been detected in wastewater, swimming pools and rivers, but not yet in drinking water. These chlorinated by-products are more stable and persistent than the parent species and further studies are needed to improve knowledge regarding their toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/25462712

“Parabens may act as weak endocrine disrupter chemicals ... Despite being used since the mid-1920s, it was only in 1996 that the first analytical results of their occurrence in water were published. Considered as emerging contaminants, it is useful to review the knowledge acquired over the last decade regarding their occurrence, fate and behavior in aquatic environments. Methylparaben and propylparaben predominate, reflecting the composition of paraben mixtures in common consumer products. Being compounds containing phenolic hydroxyl groups, parabens can react readily with free chlorine, yielding halogenated by-products. Chlorinated parabens have been detected in wastewater, swimming pools and rivers, but not yet in drinking water. These chlorinated by-products are more stable and persistent than the parent species ...”

“The assertion that individual glucocorticoid-like compounds do not produce harm because they are present at low, ineffective levels in humans may be irrelevant when we include mixed exposures. This study emphasizes that risk assessment of compounds should take mixture effects into account.”

Toxicology Letters • January 2015

Glucocorticoid-like activity of propylparaben, butylparaben, diethylhexyl phthalate and tetramethrin mixtures studied in the MDA-kb2 cell line

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Abstract

Endocrine-disrupting compounds can interfere with the endocrine organs or hormone system and cause tumors, birth defects and developmental disorders in humans. The estrogen-like activity of compounds has been widely studied but little is known concerning their possible modulation of the glucocorticoid receptor. Steroidal (synthetic and natural) and non-steroidal endocrine-active compounds commonly occur as complex mixtures in human environments. Identification of such molecular species, which are responsible for modulating the glucocorticoid receptor are necessary to fully assess their risk. We have used the MDA-kb2 cell line, which expresses endogenous glucocorticoid receptor and a stably transfected luciferase reporter gene construct, to quantify the glucocorticoid-like activity of four compounds present in products in everyday use - propylparaben (PP), butylparaben (BP), diethylhexyl phthalate (DEHP) and tetramethrin (TM). We tested all possible combinations of these compounds at two concentrations (1 μM and 10 nM) and compared their glucocorticoid-like activity. At the concentration of 1 μM seven mixtures were identified to have glucocorticoid-like activity except: DEHP+TM, BP+TM, DEHP+PP+TM, BP+PP+TM. At the concentration of 10 nM only three mixtures have glucocorticoid modulatory activity: DEHP+PP, BP+PP, DEHP+BP+PP+TM. Identified glucocorticoid-like activities were between 1.25 and 1.51 fold at the concentration of 1 μM and between 1.23 and 1.44 fold at the concentration of 10 nM in comparison with the solvent control. Individually BP, PP, and DEHP had glucocorticoid-like activity of 1.60, 1.57 and 1.50 fold over the solvent control at the concentration of 1 μM. On the other hand PP and DEHP, at the concentration of 10nM, showed no glucocorticoid-like activity, while BP showed 1.44 fold. The assertion that individual glucocorticoid-like compounds do not produce harm because they are present at low, ineffective levels in humans may be irrelevant when we include mixed exposures. This study emphasizes that risk assessment of compounds should take mixture effects into account.

http://www.ncbi.nlm.nih.gov/pubmed/25448277

Journal Of Exposure Science & Environmental Epidemiology • May 2015

Estrogenic and anti-estrogenic activity of off-the-shelf hair and skin care products

Author information

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Abstract

Use of personal care products is widespread in the United States but tends to be greater among African Americans than whites. Of special concern is the possible hazard of absorption of chemicals with estrogenic activity (EA) or anti-EA (AEA) in these products. Such exposure may have adverse health effects, especially when it occurs during developmental windows (e.g., prepubertally) when estrogen levels are low. We assessed the ethanol extracts of eight commonly used hair and skin products popular among African Americans for EA and AEA using a cell proliferation assay with the estrogen sensitive MCF-7:WS8 cell line derived from a human breast cancer. Four of the eight personal care products tested (Oil Hair Lotion, Extra-dry Skin Lotion, Intensive Skin Lotion, Petroleum Jelly) demonstrated detectable EA, whereas three (Placenta Hair Conditioner, Tea-Tree Hair Conditioner, Cocoa Butter Skin Cream) exhibited AEA. Our data indicate that hair and skin care products can have EA or AEA, and suggest that laboratory studies are warranted to investigate the in vivo activity of such products under chronic exposure conditions as well as epidemiologic studies to investigate potential adverse health effects that might be associated with use of such products.

Full text, PDF, graphs, charts and 57 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4318791/pdf/nihms647390.pdf

“Use of personal care products is widespread in the United States but tends to be greater among African Americans than whites. Of special concern is the possible hazard of absorption of chemicals with estrogenic activity or anti-estrogenic activity in these products. Such exposure may have adverse health effects, especially when it occurs during developmental windows (e.g., prepubertally) when estrogen levels are low. Our data indicate that hair and skin care products can have estrogenic activity or anti-estrogenic activity, and suggest that laboratory studies are warranted to investigate the in vivo activity of such products under chronic exposure conditions as well as epidemiologic studies to investigate potential adverse health effects that might be associated with use of such products.”

“The calculated margin of safety for adult females was 108, whereas the margin of safety for males was 444.”

Toxicology • June 2015

A case study on quantitative in vitro to in vivo extrapolation for environmental esters: Methyl-, propyl- and butylparaben

Author information

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Abstract

Parabens have been reported as potential endocrine disrupters and are widely used in consumer projects including cosmetics, foods and pharmaceuticals. We report on the development of a PBPK model for methyl-, propyl-, and butylparaben. The model was parameterized through a combination of QSAR for tissue solubility and quantitative in vitro to in vivo extrapolation (IVIVE) for hydrolysis in portals of entry including intestine and skin as well as in the primary site of metabolism, the liver. Overall, the model provided very good agreement with published time-course data in blood and urine from controlled dosing studies in rat and human, and demonstrates the potential value of quantitative IVIVE in expanding the use of human biomonitoring data in safety assessment. An in vitro based cumulative margin of safety (MOS) was calculated by comparing the effective concentrations from an in vitro assay of estrogenicity to the free paraben concentrations predicted by the model to be associated with the 95th percentile urine concentrations reported in NHANES (2009-2010 collection period). The calculated MOS for adult females was 108, whereas the MOS for males was 444.

http://www.ncbi.nlm.nih.gov/pubmed/25839974

“among investigated parabens, propylparaben appears to inhibit apoptosis in cancer cells ...”

Toxicology Letters • October 2015

Action of methyl-, propyl- and butylparaben on GPR30 gene and protein expression, cAMP levels and activation of ERK1/2 and PI3K/Akt signaling pathways in MCF-7 breast cancer cells and MCF-10A non-transformed breast epithelial cells

By AM Wróbel and Gregoraszczuk Et

Abstract

In the present study, we examined cAMP levels and activation of the MAPK/ERK1/2 and PI3K/Akt signaling pathways in response to the actions of parabens on GPR30 in MCF-7 and MCF-10A cells. Cells were exposed to methyl-, propyl- or butylparaben at a concentration of 20nM; 17-ß-estradiol (10nM) was used as a positive control. 17ß-estradiol and all tested parabens increased GPR30 gene and protein expression in MCF-7 and MCF-10A cells. No parabens affected cAMP levels in either cell line, with the exception of propylparaben in MCF-10A cells. 17ß-estradiol, propylparaben, and butylparaben increased phosphorylation of ERK1/2 in MCF-7 cells, whereas 17ß-estradiol, methyl- and butylparaben, but not propylparaben, increased phosphorylation of ERK1/2 in MCF-10A cells. Akt activation was noted only in MCF-7 cells and only with propylparaben treatment. Collectively, the data presented here point to a nongenomic mechanism of action of parabens in activation GPR30 in both cancer and non-cancer breast cell lines through ßy dimer-mediated activation of the ERK1/2 pathway, but not the cAMP/PKA pathway. Moreover, among investigated parabens, propylparaben appears to inhibit apoptosis in cancer cells through activation of Akt kinases, confirming conclusions suggested by our previously published data. Nevertheless, continuing research on the carcinogenic action of parabens is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/26253279

“We detected significant endocrine activity in two of 10 plastic teethers. Those samples leached estrogenic and/or antiandrogenic activity ... methyl-, ethyl- and propylparaben were responsible for the observed estrogenic and antiandrogenic activity in one product. The second product is likely to contain at least six different antiandrogenic compounds that remain so far unidentified.”

Journal Of Applied Toxicology • November 2015

Effect-directed identification of endocrine disruptors in plastic baby teethers

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Abstract

Concerns have been raised regarding the human health effects of endocrine disrupting chemicals (EDCs), many of which are associated with and leaching from plastics. As infants are particularly vulnerable to EDCs, we have investigated whether plastic teethers for babies represent a relevant source of exposure. Applying effect-directed analysis, we use bioassays to screen teethers, toys used to soothe a baby’s teething ache, for endocrine activity and chemical analysis to identify the causative compounds. We detected significant endocrine activity in two of 10 plastic teethers. Those samples leached estrogenic and/or antiandrogenic activity as detected in the Yeast Estrogen Screen and Yeast Antiandrogen Screen. After sample fractionation, gas chromatography-mass spectrometry non-target screening revealed that methyl-, ethyl- and propylparaben were responsible for the observed estrogenic and antiandrogenic activity in one product. The second product is likely to contain at least six different antiandrogenic compounds that remain so far unidentified. This study demonstrates that plastic teethers can be a source of infant exposure to well-established and unknown EDCs. Because of their limited value to the product, but potential toxicity, manufacturers should critically revisit the use of parabens in plastic teethers and further toys. Moreover, plastic teethers might leach EDCs that escape routine analysis and, thus, toxicological evaluation. The resulting uncertainty in product safety poses a problem to consumers, producers and regulators that remain to be resolved.

http://www.ncbi.nlm.nih.gov/pubmed/25988240

Water Research • April 2015

Personal care product preservatives: risk assessment and mixture toxicities with an industrial wastewater

Author information

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Abstract

The aquatic toxicity of eight preservatives frequently used in personal care products (PCPs) (iodopropynyl butylcarbamate, bronopol, diazolidinyl urea, benzalkonium chloride, zinc pyrithione, propylparaben, triclosan and a mixture of methylchloroisothiazolinone and methylisothiazolinone) was assessed by means of two different approaches: a battery of bioassays composed of single species tests of bacteria (Vibrio fischeri and Pseudomonas putida) and protozoa (Tetrahymena thermophila), and a whole biological community resazurin-based assay using activated sludge. The tested preservatives showed considerable toxicity in the studied bioassays, but with a marked difference in potency. In fact, all biocides except propylparaben and diazolidinyl urea had EC50 values lower than 1 mg L(-1) in at least one assay. Risk quotients for zinc pyrithione, benzalkonium chloride, iodopropynyl butylcarbamate and triclosan as well as the mixture of the studied preservatives exceeded 1, indicating a potential risk for the process performance and efficiency of municipal sewage treatment plants (STPs). These four single biocides explained more than 95% of the preservative mixture risk in all bioassays. Each individual preservative was also tested in combination with an industrial wastewater (IWW) from a cosmetics manufacturing facility. The toxicity assessment was performed on binary mixtures (preservative + IWW) and carried out using the median-effect principle, which is a special case of the concept of Concentration Addition (CA). Almost 70% of all experiments resulted in EC50 values within a factor of 2 of the values predicted by the median-effect principle (CI values between 0.5 and 2). The rest of the mixtures whose toxicity was mispredicted by CA were assessed with the alternative concept of Independent Action (IA), which showed higher predictive power for the biological community assay. Therefore, the concept used to accurately predict the toxicity of mixtures of a preservative with a complex industrial wastewater depends on degree of biological complexity.

http://www.ncbi.nlm.nih.gov/pubmed/25585550

Environmental Science And Pollution Research International • May 2014

Assessment of combined antiandrogenic effects of binary parabens mixtures in a yeast-based reporter assay

Author information

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Abstract

To date, toxicological studies of endocrine disrupting chemicals (EDCs) have typically focused on single chemical exposures and associated effects. However, exposure to EDCs mixtures in the environment is common. Antiandrogens represent a group of EDCs, which draw increasing attention due to their resultant demasculinization and sexual disruption of aquatic organisms. Although there are a number of in vivo and in vitro studies investigating the combined effects of antiandrogen mixtures, these studies are mainly on selected model compounds such as flutamide, procymidone, and vinclozolin. The aim of the present study is to investigate the combined antiandrogenic effects of parabens, which are widely used antiandrogens in industrial and domestic commodities. A yeast-based human androgen receptor (hAR) assay (YAS) was applied to assess the antiandrogenic activities of n-propylparaben (nPrP), iso-propylparaben (iPrP), methylparaben (MeP), and 4-n-pentylphenol (PeP), as well as the binary mixtures of nPrP with each of the other three antiandrogens. All of the four compounds could exhibit antiandrogenic activity via the hAR. A linear interaction model was applied to quantitatively analyze the interaction between nPrP and each of the other three antiandrogens. The isoboles method was modified to show the variation of combined effects as the concentrations of mixed antiandrogens were changed. Graphs were constructed to show isoeffective curves of three binary mixtures based on the fitted linear interaction model and to evaluate the interaction of the mixed antiandrogens (synergism or antagonism). The combined effect of equimolar combinations of the three mixtures was also considered with the nonlinear isoboles method. The main effect parameters and interaction effect parameters in the linear interaction models of the three mixtures were different from zero. The results showed that any two antiandrogens in their binary mixtures tended to exert equal antiandrogenic activity in the linear concentration ranges. The antiandrogenicity of the binary mixture and the concentration of nPrP were fitted to a sigmoidal model if the concentrations of the other antiandrogens (iPrP, MeP, and PeP) in the mixture were lower than the AR saturation concentrations. Some concave isoboles above the additivity line appeared in all the three mixtures. There were some synergistic effects of the binary mixture of nPrP and MeP at low concentrations in the linear concentration ranges. Interesting, when the antiandrogens concentrations approached the saturation, the interaction between chemicals were antagonistic for all the three mixtures tested. When the toxicity of the three mixtures was assessed using nonlinear isoboles, only antagonism was observed for equimolar combinations of nPrP and iPrP as the concentrations were increased from the no-observed-effect-concentration (NOEC) to effective concentration of 80%. In addition, the interactions were changed from synergistic to antagonistic as effective concentrations were increased in the equimolar combinations of nPrP and MeP, as well as nPrP and PeP. The combined effects of three binary antiandrogens mixtures in the linear ranges were successfully evaluated by curve fitting and isoboles. The combined effects of specific binary mixtures varied depending on the concentrations of the chemicals in the mixtures. At low concentrations in the linear concentration ranges, there was synergistic interaction existing in the binary mixture of nPrP and MeP. The interaction tended to be antagonistic as the antiandrogens approached saturation concentrations in mixtures of nPrP with each of the other three antiandrogens. The synergistic interaction was also found in the equimolar combinations of nPrP and MeP, as well as nPrP and PeP, at low concentrations with another method of nonlinear isoboles. The mixture activities of binary antiandrogens had a tendency towards antagonism at high concentrations and synergism at low concentrations.

http://www.ncbi.nlm.nih.gov/pubmed/24469767

“Neonates in NICUs in Brazil are exposed to a wide variety of harmful excipients and Potentially Harmful Excipients with unpredictable results. Safer alternatives are needed ...”

European Journal Of Pediatrics • July 2014

Toxic excipients in medications for neonates in Brazil

Author information

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Abstract

The aim was to describe the exposure to excipients among neonates hospitalised in the neonatal intensive care unit (NICU) of a public hospital in Brasilia, Brazil. This was a retrospective study based on medicines that were prescribed electronically to neonates (≤28 days) who were admitted to the NICU of a hospital in Brasilia between January 1 and March 31, 2012. Excipients were identified from the medicine package leaflets and were classified according to toxicity. Seventy-nine infants received a total of 1,303 prescriptions comprising 77 formulations and 70 active drugs. Eighty-six excipients were identified, of which, 9 were harmful excipients (HE) and 48 were potentially harmful excipients (PHE). Almost all the neonates (98.7 %) were exposed to at least one HE and PHE. Preterm neonates (n=64; 1,502 neonate days) presented high risk of exposure to polysorbate 80 (3.26/100 neonate days), sodium hydroxide (3.39), PG (3.19) and propylparaben (3.06). Full-term neonates (n=15; 289 neonate days) presented risks in relation to phenol (4.84), ethanol (3.8) and sodium citrate (3.46).

CONCLUSION

Neonates in NICUs in Brazil are exposed to a wide variety of HE and PHE with unpredictable results. Safer alternatives are needed, as well as further studies on the subject.

http://www.ncbi.nlm.nih.gov/pubmed/24500397

“Experiments performed with dechlorinated water, ultrapure water, and tap water showed that under UV-light, the presence of even low levels of free chlorine, increases the photodegradation rate of target preservatives, enhancing the formation of halogenated photoproducts. Monobrominated, dibrominated and bromochlorinated hydroxybenzoates were identified, and the transformation of benzoates into halogenated parabens was also confirmed.”

The Journal Of Chromatography • July 2014

Identification of halogenated photoproducts generated after ultraviolet-irradiation of parabens and benzoates in water containing chlorine by solid-phase microextraction and gas chromatography-mass spectrometry

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Abstract

This work presents a new solid-phase microextraction (SPME)-based approach to investigate the formation of halogenated by-products generated by the UV-induced photodegradation of parabens and their congener benzoates in water containing chlorine. Degradation of parent species, and further identification of their transformation by-products were monitored by gas chromatography coupled to mass spectrometry (GC/MS). In order to improve detectability, SPME was applied as a preconcentration step after UV-irradiation of target preservatives. Experiments performed with dechlorinated water, ultrapure water, and tap water showed that under UV-light, the presence of even low levels of free chlorine, increases the photodegradation rate of target preservatives, enhancing the formation of halogenated photoproducts. Monobrominated, dibrominated and bromochlorinated hydroxybenzoates were identified, and the transformation of benzoates into halogenated parabens was also confirmed. Bromination is expected to occur when free chlorine is present, due to the presence of traces of bromide in water samples. Five halogenated phenols (mainly brominated) were detected as breakdown photoproducts from both families of target preservatives. On the basis of the appearance of the aforementioned by-products, a tentative transformation pathway, consistent with the photoformation-photodecay kinetics of the by-products, is proposed herein for the first time.

http://www.ncbi.nlm.nih.gov/pubmed/24856965

“This is the first report that in vitro, parabens can influence not only proliferation but also migratory and invasive properties of human breast cancer cells.”

Journal Of Applied Toxicology • September 2014

Exposure to parabens at the concentration of maximal proliferative response increases migratory and invasive activity of human breast cancer cells in vitro

Author information

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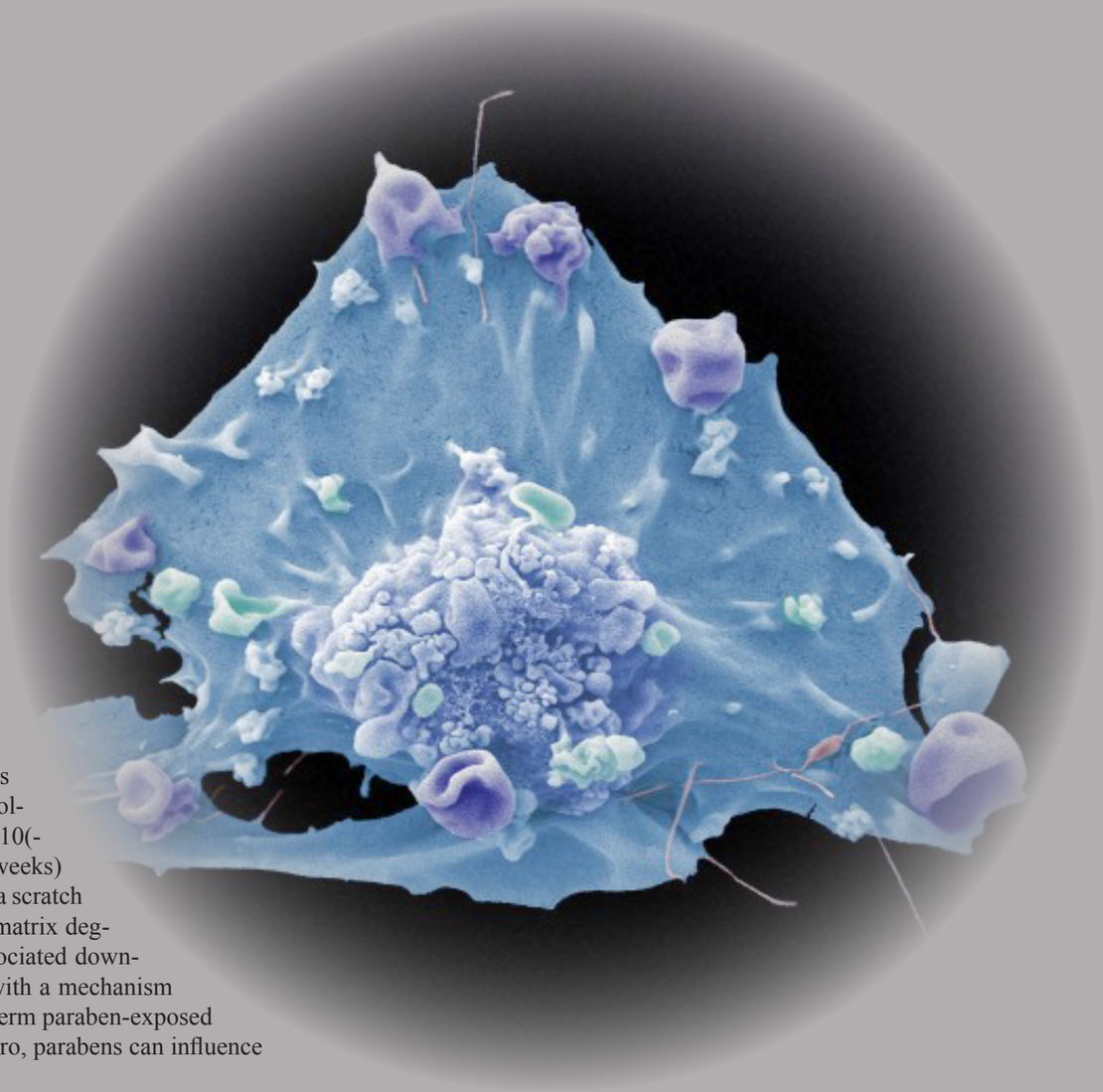
Abstract

Alkyl esters of p-hydroxybenzoic acid (parabens) are widely used as preservatives in personal care products, foods and pharmaceuticals. Their oestrogenic activity, their measurement in human breast tissue and their ability to drive proliferation of oestrogen-responsive human breast cancer cells has opened a debate on their potential to influence breast cancer development. As proliferation is not the only hallmark of cancer cells, we have investigated the effects of exposure to parabens at concentrations of maximal proliferative response on migratory and invasive properties using three oestrogen-responsive human breast cancer cell lines (MCF-7, T-47-D, ZR-75-1). Cells were maintained short-term (1 week) or long-term (20 ± 2 weeks) in phenol-red-free medium containing 5% charcoal-stripped serum with no addition, 10(-8) M 17ß-oestradiol, 1-5 × 10(-4) M methylparaben, 10(-5) M n-propylparaben or 10(-5) M n-butylparaben. Long-term exposure (20 ± 2 weeks) of MCF-7 cells to methylparaben, n-propylparaben or n-butylparaben increased migration as measured using a scratch assay, time-lapse microscopy and xCELLigence technology: invasive properties were found to increase in matrix degradation assays and migration through matrigel on xCELLigence. Western immunoblotting showed an associated down-regulation of E-cadherin and ß-catenin in the long-term paraben-exposed cells which could be consistent with a mechanism involving epithelial to mesenchymal transition. Increased migratory activity was demonstrated also in long-term paraben-exposed T-47-D and ZR-75-1 cells using a scratch assay and time-lapse microscopy. This is the first report that in vitro, parabens can influence not only proliferation but also migratory and invasive properties of human breast cancer cells.

http://www.ncbi.nlm.nih.gov/pubmed/24652746



A breast cancer cell under scanning electron micrograph
Photo by Anne Weston

“Methylparaben increased pro-survival gene. Butylparaben increased BCL2L1 gene, as did 17ß-estradiol, while propylparaben upregulated both the extrinsic and intrinsic apoptotic pathways.”

Journal Of Applied Toxicology • September 2014

Differential effect of methyl-, butyl- and propylparaben and 17ß-estradiol on selected cell cycle and apoptosis gene and protein expression in MCF-7 breast cancer cells and MCF-10A non-malignant cells

Author information

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Abstract

Parabens are alkyl esters of p-hydroxybenzoic acid used widely as antimicrobial preservatives in consumer products, including pharmaceuticals, foods and cosmetics. We showed previously that methyl-, butyl- and propylparaben parabens, even at low doses, stimulate the proliferation of MCF-7 breast cancer cells and non-transformed MCF-10A breast epithelial cells. The present study was undertaken to determine whether this represents a direct effect on cell cycle and apoptotic gene expression. MCF-7 and MCF-10A cells were exposed to methyl, butyl- and propylparaben (20 nm) or 17ß-estradiol (10 nm). Cell cycle and apoptotic gene expression were evaluated by real-time polymerase chain reaction and protein expression by Western blot. 17ß-estradiol upregulated G1 /S phase genes and downregulated cell cycle progression inhibitors in both MCF-7 and MCF-10A. Up-regulation of Bcl-xL and downregulation of caspase 9 was observed in MCF-7, while upregulation of Bcl-xL, BCL2L2 and caspase 9 was noted in MCF-10A. Cyclins in MCF-7 cells were not affected by any of the parabens. Methyl- and butylparaben had no effect on the expression of selected apoptotic genes in MCF-7. In MCF-10A, all parabens tested increased the expression of G1 /S phase genes, and downregulated cell cycle inhibitors. Methylparaben increased pro-survival gene. Butylparaben increased BCL2L1 gene, as did 17ß-estradiol, while propylparaben upregulated both the extrinsic and intrinsic apoptotic pathways. There are differences in cell cycle and apoptosis gene expression between parabens and 17ß-estradiol in MCF-7 cells. In MCF-10A cells, most of the genes activated by parabens were comparable to those activated by 17s-estradiol.

http://www.ncbi.nlm.nih.gov/pubmed/24481588

“We demonstrated that binary mixtures of both chemicals induce greater cytotoxic effects than those reported after single exposure to each compound [alone].”

Food Chemistry Toxicology • October 2014

The antioxidant butylated hydroxyanisole potentiates the toxic effects of propylparaben in cultured mammalian cells

Author information

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Abstract

Butylated hydroxyanisole and propylparaben are phenolic preservatives commonly used in food, pharmaceutical and personal care products. Both chemicals have been subjected to extensive toxicological studies, due to the growing concern regarding their possible impacts on environmental and human health. However, the cytotoxicity and underlying mechanisms of co-exposure to these compounds have not been explored. In this study, a set of relevant cytotoxicity endpoints including cell viability and proliferation, oxidative stress, DNA damage and gene expression changes were analyzed to assess whether the antioxidant butylated hydroxyanisole could prevent the pro-oxidant effects caused by propylparaben in Vero cells. We demonstrated that binary mixtures of both chemicals induce greater cytotoxic effects than those reported after single exposure to each compound. Simultaneous treatment with butylated hydroxyanisole and propylparaben caused G0/G1 cell cycle arrest as a result of enhanced generation of oxidative stress and DNA double strand breaks. DNA microarray analysis revealed that a cross-talk between transforming growth factor beta (TGFß) and ataxia-telangiectasia mutated kinase (ATM) pathways regulates the response of Vero cells to the tested compounds in binary mixture. Our findings indicate that butylated hydroxyanisole potentiates the pro-oxidant effects of propylparaben in cultured mammalian cells and provide useful information for their safety assessment.

http://www.ncbi.nlm.nih.gov/pubmed/25086368

“Our results suggest that parabens may contribute to [the] obesity epidemic ...”

Toxicology Science • January 2013

Effects of parabens on adipocyte differentiation

Author information

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Abstract

Parabens are a group of alkyl esters of p-hydroxybenzoic acid that include methylparaben, ethylparaben, propylparaben, butylparaben, and benzylparaben. Paraben esters and their salts are widely used as preservatives in cosmetics, toiletries, food, and pharmaceuticals. Humans are exposed to parabens through the use of such products from dermal contact, ingestion, and inhalation. However, research on the effects of parabens on health is limited, and the effects of parabens on adipogenesis have not been systematically studied. Here, we report that (1) parabens promote adipogenesis (or adipocyte differentiation) in murine 3T3-L1 cells, as revealed by adipocyte morphology, lipid accumulation, and mRNA expression of adipocyte-specific markers; (2) the adipogenic potency of parabens is increased with increasing length of the linear alkyl chain in the following potency ranking order: methyl- < ethyl- < propyl- < butylparaben. The extension of the linear alkyl chain with an aromatic ring in benzylparaben further augments the adipogenic ability, whereas 4-hydroxybenzoic acid, the common metabolite of all parabens, and the structurally related benzoic acid (without the OH group) are inactive in promoting 3T3-L1 adipocyte differentiation; (3) parabens activate glucocorticoid receptor and/or peroxisome proliferator-activated receptor □ in 3T3-L1 preadipocytes; however, no direct binding to, or modulation of, the ligand binding domain of the glucocorticoid receptor by parabens was detected by glucocorticoid receptor competitor assays; and lastly, (4) parabens, butyl- and benzylparaben in particular, also promote adipose conversion of human adipose-derived multipotent stromal cells. Our results suggest that parabens may contribute to obesity epidemic, and the role of parabens in adipogenesis in vivo needs to be examined further.

Full text, graphs, charts and 52 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3621350/

“In the present study, we report that parabens can induce anchorage-independent growth of MCF-10A immortalized but non-transformed human breast epithelial cells, a property closely related to transformation and a predictor of tumour growth in vivo ... To our knowledge, this is the first study to report that parabens can induce a transformed phenotype in human breast epithelial cells in vitro, and further investigation is now justified into a potential link between parabens and breast carcinogenesis.”

Journal Of Applied Toxicology • May 2013

Parabens enable suspension growth of MCF-10A immortalized, non-transformed human breast epithelial cells

Author information

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Abstract

Parabens (alkyl esters of p-hydroxybenzoic acid) are used extensively as preservatives in consumer products, and intact esters have been measured in several human tissues. Concerns of a potential link between parabens and breast cancer have been raised, but mechanistic studies have centred on their oestrogenic activity and little attention has been paid to any carcinogenic properties. In the present study, we report that parabens can induce anchorage-independent growth of MCF-10A immortalized but non-transformed human breast epithelial cells, a property closely related to transformation and a predictor of tumour growth in vivo. In semi-solid methocel suspension culture, MCF-10A cells produced very few colonies and only of a small size but the addition of $5 \times 10(-4)$ M methylparaben, 10(-5) M n-propylparaben or 10(-5) M n-butylparaben resulted in a greater number of colonies per dish ($P<0.05$ in each case) and an increased average colony size ($P<0.001$ in each case). Dose-responses showed that concentrations as low as 10(-6) M methylparaben, 10(-7) M n-propylparaben and 10(-7) M n-butylparaben could increase colony numbers ($P=0.016$, $P=0.010$, $P=0.008$, respectively): comparison with a recent measurement of paraben concentrations in human breast tissue samples from 40 mastectomies (Barr et al., 2012) showed that 22/40 of the patients had at least one of the parabens at the site of the primary tumour at or above these concentrations. To our knowledge, this is the first study to report that parabens can induce a transformed phenotype in human breast epithelial cells in vitro, and further investigation is now justified into a potential link between parabens and breast carcinogenesis.

http://www.ncbi.nlm.nih.gov/pubmed/22744862

“Our results showed that propyl paraben [has] ... cytotoxic mechanisms (high apoptosis and necrosis levels only at the test concentration of 1%).”

International Journal Of Cosmetic Science • April 2012

In vitro induction of apoptosis, necrosis and genotoxicity by cosmetic preservatives: application of flow cytometry as a complementary analysis by NRU

Author information

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Abstract

Preservatives are used in cosmetics to prevent microbial contamination; however, some preservatives are not free of allergenic and cytotoxic potential. Allergenicity and cytotoxicity potential values are major aspects of preservative safety, which determine limitations and maximum concentration dose in a cosmetic product. The purpose of this study was to investigate and compare the in vitro apoptosis, necrosis and genotoxicity-inducing potential of five different types of preservatives: Phenoxyethanol (PE), Propylparaben (PP), Methylparaben (MP), Benzyl Alcohol (BA) and Ethylhexyl Glycerine (EG). In vitro experiments were carried out on human dermal fibroblasts by a quantitative flow cytometry method, using specific cell markers (Annexin V, Propidium Iodide and H2AX). We compared the resulting cell viability by means of neutral red uptake (NRU) and established the IC(50) . Our results showed that PE, PP, MP and BA have similar cytotoxic mechanisms (high apoptosis and necrosis levels only at the test concentration of 1%), whereas EG showed only an apoptosis pathway. For genotoxicity, both parabens yielded the highest values. Results obtained by flow cytometry for necrosis were comparable to those produced by NRU; however, NRU does not distinguish apoptosis from necrosis. We propose that flow cytometry is a more sophisticated methodology for understanding the cytotoxic mechanisms of cosmetic preservatives and can be used to complement the NRU.

http://www.ncbi.nlm.nih.gov/pubmed/22118339

“These observations suggest that highly exposed population groups, especially women of reproductive age, may not be protected sufficiently against the combined effects of chemicals that affect the hormonal milieu required for normal male sexual differentiation.”

The Journal Of The Society For Reproduction And Fertility • June 2012

Mixtures of endocrine disrupting contaminants modelled on human high end exposures: an exploratory study in rats

Author information

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Abstract

By diminishing the action of androgens during gestation, certain chemicals can induce irreversible demasculinization and malformations of sex organs in the male rat after gestational exposure. Studies with mixtures of such anti-androgens have shown that substantial combined effects occur even though each individual chemical is present at low, ineffective doses, but the effects of mixtures modelled based on human intakes have not previously been investigated. To address this issue for the first time, we selected 13 chemicals for a developmental mixture toxicity study in rats where data about in vivo endocrine disrupting effects and information about human exposures was available, including phthalates, pesticides, UV-filters, bisphenol A, parabens and the drug paracetamol. The mixture ratio was chosen to reflect high end human intakes. To make decisions about the dose levels for studies in the rat, we employed the point of departure index (PODI) approach, which sums up ratios between estimated exposure levels and no-observed-adverse-effect-level (NOAEL) values of individual substances. For high end human exposures to the 13 selected chemicals, we calculated a PODI of 0.016. As only a PODI exceeding 1 is expected to lead to effects in the rat, a total dose more than 62 times higher than human exposures should lead to responses. Considering the high uncertainty of this estimate, experience on lowest-observed-adverse-effect-level (LOAEL)/NOAEL ratios and statistical power of rat studies, we expected that combined doses 150 times higher than high end human intake estimates should give no, or only borderline effects, whereas doses 450 times higher should produce significant responses. Experiments indeed showed clear developmental toxicity of the 450-fold dose in terms of increased nipple retention (NR) and reduced ventral prostate weight. The 150-fold dose group exhibited significantly increased NR. These observations suggest that highly exposed population groups, especially women of reproductive age, may not be protected sufficiently against the combined effects of chemicals that affect the hormonal milieu required for normal male sexual differentiation.

Full text, graphs, charts and 72 references

http://www.reproduction-online.org/content/147/4/489.full.pdf+html

“Overall, the estrogenic burden of parabens and their metabolites in blood may exceed the action of endogenous estradiol in childhood and the safety margin for propylparaben is very low when comparing worst-case exposure to NOAELs from experimental studies in rats and mice.”

Reproductive Toxicology • September 2010

Possible endocrine disrupting effects of parabens and their metabolites

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Abstract

Parabens are preservatives used in a wide range of cosmetic products, including products for children, and some are permitted in foods. However, there is concern for endocrine disrupting effects. This paper critically discusses the conclusions of recent reviews and original research papers and provides an overview of studies on toxicokinetics. After dermal uptake, parabens are hydrolyzed and conjugated and excreted in urine. Despite high total dermal uptake of paraben and metabolites, little intact paraben can be recovered in blood and urine. Paraben metabolites may play a role in the endocrine disruption seen in experimental animals and studies are needed to determine human levels of parabens and metabolites. Overall, the estrogenic burden of parabens and their metabolites in blood may exceed the action of endogenous estradiol in childhood and the safety margin for propylparaben is very low when comparing worst-case exposure to NOAELs from experimental studies in rats and mice.

http://www.ncbi.nlm.nih.gov/pubmed/20381602

NOAELs

The “No-Observed-Adverse-Effect-Level” is considered an important part of non-clinical risk assessments. Because NOAEL is a professional opinion based on a particular study(s) design, indications of the drug, anticipated pharmacology and what can be a wide array of both negative and positive effects that weren’t original targets, there is no specific standard definition of NOAEL. It’s an opinion.

“Our results demonstrate that exposure to the compound for 24h causes changes in cell-proliferation rates rather than in cell viability. A significant and dose-dependent decline in the percentage of mitotic cells was observed at the lowest concentration tested, mainly due to cell-cycle arrest ...”

Mutation Research • September 2010

Oxidative DNA damage contributes to the toxic activity of propylparaben in mammalian cells

Author information

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Abstract

Propyl p-hydroxybenzoate, commonly referred to as propylparaben, is the most frequently used preservative to inhibit microbial growth and extend shelf life of a range of consumer products. The objective of this study was to provide further insight into the toxicological profile of this compound, because of the current discrepancy in the literature with regard to the safety of parabens. The Vero cell line, derived from the kidney of the green monkey, was selected to evaluate the adverse effects of propylparaben by use of a set of mechanistically relevant endpoints for detecting cytotoxicity and genotoxic activities. Our results demonstrate that exposure to the compound for 24h causes changes in cell-proliferation rates rather than in cell viability. A significant and dose-dependent decline in the percentage of mitotic cells was observed at the lowest concentration tested, mainly due to cell-cycle arrest at the G0/G1 phase. Immunodetection techniques revealed that induction of DNA double-strand breaks and oxidative damage underlies the cytostatic effect observed in treated Vero cells. Additional studies are in progress to extend these findings, which define a novel mode of action of propylparaben in cultured mammalian cells.

http://www.ncbi.nlm.nih.gov/pubmed/20682357

Reproductive Toxicology • January 2009

Parabens in male infertility-is there a mitochondrial connection?

Author information

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Abstract

“Parabens are widely used as preservatives in many foods, cosmetics, toiletries, and pharmaceuticals due to their relatively low toxicity profile and to a long history of safe use. Parabens are alkyl esters of p-hydroxybenzoic acid and typically include methylparaben, ethylparaben, propylparaben, butylparaben, isobutylparaben, isopropylparaben and benzylparaben. These compounds are known to have a null or very weak estrogenic activity in estrogen receptor assays in vitro. In recent years, an increasing concern has emerged regarding possible adverse effects of chemicals in food and in cosmetics on human reproduction outcomes. In developed countries about 15% of human couples are affected by infertility, almost half of these cases attributed to men, through low sperm motility or/and sperm count. It is known that a significant number of cases of male infertility results from exposure to xenobiotics, and also that testis mitochondria are particularly affected by drug-induced toxicity. The present review discusses evidence that parabens may not be as safe as initially thought, and suggests that the interaction between parabens and mitochondrial function in the testis may be key in explaining the contribution of parabens for a decrease in reproductive potential.”

http://www.ncbi.nlm.nih.gov/pubmed/19007877

PARABENS MAY NOT BE SAFE AS ONCE THOUGHT

“This paper describes the application of the basic principles of ‘Hurdle Technology’ in the production of self-preserving cosmetics. Multifunctional antimicrobial ingredients and plant-derived essential oils and extracts that are used as alternative or natural preservatives and are not listed in Annex VI of the Cosmetic Directive are also reported.”

International Journal Of Cosmetic Science • June 2009

Self-preserving cosmetics

By A. Varvaresou, et al.

Abstract

Preservatives are added to products for two reasons: first, to prevent microbial spoilage and therefore to prolong the shelf life of the product; second, to protect the consumer from a potential infection. Although chemical preservatives prevent microbial growth, their safety is questioned by a growing segment of consumers. Therefore, there is a considerable interest in the development of preservative-free or self-preserving cosmetics. In these formulations traditional/chemical preservatives have been replaced by other cosmetic ingredients with antimicrobial properties that are not legislated as preservatives according to the Annex VI of the Commission Directive 76/768/EEC and the amending directives (2003/15/EC, 2007/17/EC and 2007/22/EC). ‘Hurdle Technology’, a technology that has been used for the control of product safety in the food industry since 1970s, has also been applied for the production of self-preserving cosmetics. ‘Hurdle Technology’ is a term used to describe the intelligent combination of different preservation factors or hurdles to deteriorate the growth of microorganisms. Adherence to current good manufacturing practice, appropriate packaging, careful choice of the form of the emulsion, low water activity and low or high pH values are significant variables for the control of microbial growth in cosmetic formulations. This paper describes the application of the basic principles of ‘Hurdle Technology’ in the production of self-preserving cosmetics. Multifunctional antimicrobial ingredients and plant-derived essential oils and extracts that are used as alternative or natural preservatives and are not listed in Annex VI of the Cosmetic Directive are also reported.

Full text, PDF, graphs, charts and 74 references at the link below

http://onlinelibrary.wiley.com/doi/10.1111/j.1468-2494.2009.00492.x/abstract;jsessionid=12B423F0D7C4020C1B1ECCF2847CD5AF.f03t04

“In a previous study, it was demonstrated by the present author that exposure of post-weaning mammals to butyl paraben adversely affects the secretion of testosterone and the function of the male reproductive system. In the present study, it is shown that propyl paraben also adversely affects the hormonal secretion and the male reproductive functions. Daily sperm production and its efficiency in the testis of all groups receiving propyl paraben significantly decreased ... at dose of 0.10% and above.”

Food Chemistry And Toxicology • December 2002

Effects of propyl paraben on the male reproductive system

By S. Oishi
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Abstract

Parabens are p-hydroxybenzoic acid ester compounds widely used as preservatives in foods, cosmetics, toiletries and pharmaceuticals. These compounds exert a weak estrogenic activity as determined by in vitro estrogen receptor assay and in vivo uterotrophic assay. In a previous study, it was demonstrated by the present author that exposure of post-weaning mammals to butyl paraben adversely affects the secretion of testosterone and the function of the male reproductive system. In the present study, it is shown that propyl paraben also adversely affects the hormonal secretion and the male reproductive functions. Propyl paraben was administered to 3-week-old rats which were divided into four groups of eight animals each, at doses of 0.00, 0.01, 0.10 and 1.00% with the AIN93G modified diet. At the end of 4 weeks, the rats were sacrificed by decapitation and the weights of testes, epididymides, prostates, seminal vesicles and preputial glands were determined. There were no treatment-related effects of propyl paraben on the organ weights in any of the study groups. The cauda epididymal sperm reserves and concentrations decreased in a dose-dependent manner and the difference was significant at dose of 0.10% and above. Daily sperm production and its efficiency in the testis of all groups receiving propyl paraben significantly decreased. The serum testosterone concentration decreased in a dose-dependent manner and the decrease was significant in the group that received the highest dose. The exposure level at which this effect was observed is the same as the upper-limit acceptable daily intake (10 mg/kg body weight/day) of parabens in the European Community and Japan.

http://www.ncbi.nlm.nih.gov/pubmed/12419695

“Both compounds [methyl- and propyl paraben] are shown to be ciliotoxic at concentrations equal to or lower than those in use for preserving aqueous formulations.”

Journal Of Pharmacy And Pharmacology • October 1993

Ciliotoxicity of methyl- and propyl-p-hydroxybenzoates: a dose-response and surface-response study

Author information

By L. Jian1 amd A. Li Wan Po, Drug Delivery Research Group, School of Pharmacy, Queen’s University of Belfast, UK

Abstract

The effect of methyl-p-hydroxybenzoate (methyl paraben, MHB) and propyl-p-hydroxybenzoate (propyl paraben, PHB) on ciliary beat frequency was investigated using surface-response methodology. Both compounds are shown to be ciliotoxic at concentrations equal to or lower than those in use for preserving aqueous formulations. The dose-response curves show the typical sigmoidal pattern. Interaction by the two compounds is evidenced by the curved response surface for ciliotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/7904636

“Potent in vitro spermicidal activity of parabens against human spermatozoa was demonstrated in this study.”

Contraception • March 1989

In vitro spermicidal activity of parabens against human spermatozoa

Author information
Song BL1, Li HY, Peng DR
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People’s Republic of China

Abstract

Potent in vitro spermicidal activity of parabens against human spermatozoa was demonstrated in this study. The “pass” point concentration of the four parabens--methylparaben, ethylparaben, propylparaben, and butylparaben, at which all spermatozoa were immobilized and no immobilized spermatozoon revived after 30 min incubation in phosphate buffered glucose solution, was 6, 8, 3, and 1 mg/ml, respectively, as tested by Harris’ method. These parabens are used as food and pharmaceutic preservatives; less toxicity and side effects were expected for the development of parabens as vaginal contraceptive agents.

http://www.ncbi.nlm.nih.gov/pubmed/2714092

“Profound dose-dependent changes consisting of intercellular vacuolization and thickening of the endothelial layer were noted within 1 day following administration of solutions that contained sodium bisulfite ormethylparaben and propylparaben.

These changes are of concern because these agents are present in many preparations used to treat a wide variety of eye diseases.”

Investigative Ophthalmology & Visual Science • April 1986

Subconjunctival injections. Preservative-related changes in the corneal endothelium

Weinreb RN, Wood I, Tomazzoli L, Alvarado J.

Abstract

The morphologic effects on rabbit corneal endothelium of several common ophthalmic vehicle constituents were examined following subconjunctival administration. Profound dose-dependent changes consisting of intercellular vacuolization and thickening of the endothelial layer were noted within 1 day following administration of solutions that contained sodium bisulfite or methylparaben and propylparaben. These changes persisted for at least 5 days except in those eyes treated with the lowest concentration of sodium bisulfite. In contrast, administration of sodium citrate and creatinine or unpreserved normal saline resulted in only minimal effects. These changes are of concern because these agents are present in many preparations used to treat a wide variety of eye diseases.

http://www.ncbi.nlm.nih.gov/pubmed/3957570

“Mixtures of parabens are not superior except when multiple saturation is possible. In overall performance only methyl paraben appears to be a good preservative.”

Journal Of The Society Of Cosmetology And Chemistry • May 1981

The Parabens: Bacterial Adaptation and Preservative Capacity

By John J O’Neill and Catherine A. Meade

AVON

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Synopsis

The initial rates of kill of Escherichia coli by methyl, ethyl and propyl parabens are similar at equal saturation fraction in a buffered salts-glucose medium. This is expected from the Ferguson Principle of equal activity of homologs, but the survival curves soon diverge strongly, apparently because the rate of adaptation increases markedly with increasing molecular weight; E. coli adapts readily to propyl paraben, hardly at all to methyl. As a result, the parabens clearly rank methyl> ethyl> propyl> butyl> benzyl in their antimicrobial capacities at equal saturation fraction. The same ranking holds when equal weight concentration are challenged with other bacteria in oil/water emulsions and in a shampoo base. Performance in these systems is discussed in terms of apparent solubilities. Mixtures of parabens are not superior except when multiple saturation is possible. In overall performance only methyl paraben appears to be a good preservative.

http://www.journal.scconline.org/pdf/cc1982/cc033n02/p00075-p00084.pdf

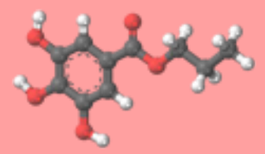
CHAPTER TWELVE

Propyl Gallate

The Peer Review

Propyl gallate, or propyl 3,4,5-trihydroxybenzoate, is an ester formed by the condensation of gallic acid and propanol. Since 1948, this antioxidant has been added to foods containing oils and fats to prevent oxidation. As a food additive, it's used under the E number E310. Propyl Gallate is not a super popular additive and you won't find it in many products. Go over the ingredient list of suspect products and if propyl gallate is an ingredient, don't buy it.

Propyl gallate is an antioxidant. It protects against oxidation by hydrogen peroxide and oxygen free radicals so it has medically valuable qualities. Propyl gallate is used to protect oils and fats in products from oxidation; it is used in foods, cosmetics, hair products, adhesives, and lubricants.



Propyl gallate is used as a preservative in products that contain edible fats, such as sausage and lard but you won't find many sausage makers or lard manufacturers that still use it. It's classified as generally regarded as safe (GRAS) even though a National Toxicology Program study reported an association with tumors in male rats and rare brain tumors in two female rats (NTP 1982). These findings do not establish a causal link between propyl gallate and cancer, but they raise important questions about whether this chemical should be considered safe. A 2014 opinion by the European Food Safety Authority concluded that the available reproductive studies on propyl gallate are outdated and poorly described. In addition, there is incomplete data on whether propyl gallate is an endocrine disruptor; some evidence suggests it may have estrogenic activity (EFSA 2014; Amadasi 2009; ter Veld 2006). A 2009 study included here found that propyl gallate acts as an estrogen antagonist

1. Propyl Gallate is an artificial food additive, that is also used in cosmetics and pharmaceuticals.
2. It is a whitish crystalline powder.
3. You may find propyl gallate in meat products, microwaveable popcorn, soup mixes, chewing gum, mayonnaise, and frozen meals.
4. It has antioxidant properties, which means it helps stop oxygen molecules from mixing with the oil in food, causing the food to go rancid.
5. Propyl gallate is also denoted E310.
6. Some studies on rats have shown that propyl gallate may cause cancer.
7. Other side effects of consumption are stomach and skin irritability, as well as allergic reactions that impact breathing.
8. It may also cause kidney and liver problems.
9. In some cases, to improve its efficacy, propyl gallate is used in conjunction with 2 other preservatives – BHA and BHT, which are also suspect as carcinogenic.
10. Although the FDA considers propyl gallate safe, in other countries it is either banned or very limited in use.

New research suggests as a dog food preservative propyl gallate may be responsible for causing a potentially dangerous health issue for dogs. That's because of the chemical's unique ability to mimic the negative effects of the female hormone, estrogen. Although the FDA insists the agent can be considered safe, recent studies have linked propyl gallate with a special group of hormone-like compounds known as xenoestrogens.

Xenoestrogens have the potential to adversely affect reproductive health. In humans, they have the ability to transform a normal breast cell into a cancer cell. Propyl gallate can also affect a developing fetus as well as decrease the sperm count in males. Feeding a dog the same chemical additive—not just occasionally, but with every meal—certainly favors the creation of problems associated with long term exposure to any toxic substance.

Propyl Gallate can cause allergic reactions in the form of an asthma attack in some people. It can also cause stomach and skin irritation, liver damage, kidney damage and has the potential to increase your chances of having cancer. Propyl Gallate is a dangerous drug.

“Consistent with these findings, propyl gallate and 9-AA both suppressed CPT-induced G2/M cell-cycle arrest and increased the number of abnormal nuclei. Our results suggest that early DDR-inhibitory effects of propyl gallate and 9-AA contribute to their chromosome damaging potential ...”

Toxicology Sciences • February 2016

Disruption of DNA Damage-response by Propyl Gallate and 9-Aminoacridine

Author information

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Abstract

The DNA-damage response (DDR) protects the genome from various types of endogenous and exogenous DNA damage, and can itself be a target of certain chemicals that give rise to chromosomal aberrations. Here, we developed a screening method to detect inhibition of MDC1 foci formation (the EGFP-MDC1 foci formation-inhibition assay) using EGFP-MDC1-expressing human cells. The assay identified propyl gallate (PG) and 9-aminoacridine (9-AA) as inhibitors of camptothecin (CPT)-induced MDC1 foci formation. We demonstrated that the inhibition of CPT-induced MDC1 foci formation by PG was caused by the direct suppression of histone H2AX phosphorylation at Ser139 (yH2AX), which is required for MDC1 foci formation, by quantifying yH2AX in cells and in vitro. 9-AA also directly suppressed H2AX Ser139-phosphorylation in vitro but the concentration was much higher than that required to suppress CPT-induced MDC1 foci formation in cells. Consistent with these findings, PG and 9-AA both suppressed CPT-induced G2/M cell-cycle arrest and increased the number of abnormal nuclei. Our results suggest that early DDR-inhibitory effects of PG and 9-AA contribute to their chromosome-damaging potential, and that the EGFP-MDC1 foci formation-inhibition assay is useful for detection of and screening for H2AX Ser139-phosphorylation-inhibitory effects of chemicals.

http://www.ncbi.nlm.nih.gov/pubmed/26928355

“Taken together, these results suggest a novel effect of Propyl Gallate on adipocyte differentiation in hAMSCs, supporting a negative role of ERK1/2 pathway in adipogenic differentiation.”

Molecules And Cells • April 2015

Propyl gallate inhibits adipogenesis by stimulating extracellular signal-related kinases in human adipose tissue-derived mesenchymal stem cells

Author information

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4. Department of Food Nutrition and Cook, Daegu Science University, Daegu 702-723, Korea

Abstract

Propyl gallate (PG) used as an additive in various foods has antioxidant and anti-inflammatory effects. Although the functional roles of PG in various cell types are well characterized, it is unknown whether PG has effect on stem cell differentiation. In this study, we demonstrated that PG could inhibit adipogenic differentiation in human adipose tissue-derived mesenchymal stem cells (hAMSCs) by decreasing the accumulation of intracellular lipid droplets. In addition, PG significantly reduced the expression of adipocyte-specific markers including peroxisome proliferator-activated receptor-y (PPAR-y), CCAAT enhancer binding protein-a (C/EBP-s), lipoprotein lipase (LPL), and adipocyte fatty acid-binding protein 2 (aP2). PG inhibited adipogenesis in hAMSCs through extracellular regulated kinase (ERK) pathway. Decreased adipogenesis following PG treatment was recovered in response to ERK blocking. Taken together, these results suggest a novel effect of PG on adipocyte differentiation in hAMSCs, supporting a negative role of ERK1/2 pathway in adipogenic differentiation.

Full text, graphs, charts and 41 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4400308/

“Exploring the radical scavenging and reducing properties of antioxidantsespecially those which are found naturally in plant sources are of great interest due to their protective roles in biological systems.”

Journal Of Food Science And Technology • September 2015

Reactivity of phenolic compounds towards free radicals under in vitro conditions

Author information

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2. Chemical Science and Technology Division, National Institute of Interdisciplinary Science and Technology, (NIIST, CSIR), Trivandrum, 695019 Kerala India
3. Institute of Bioproduct Development, Universiti Teknologi Malaysia, 81310 Johor Bahru, Johor Malaysia

Abstract

The free radical scavenging activity and reducing power of 16 phenolic compounds including four hydroxycinnamic acid derivatives namely ferulic acid, caffeic acid, sinapic acid and p-coumaric acid, benzoic acid and its derivatives namely protocatechuic acid, gallic acid and vanillic acid, benzene derivatives namely vanillin, vanillyl alcohol, veratryl alcohol, veratraldehyde, pyrogallol, guaiacol and two synthetic antioxidants, butylated hydroxy anisole (BHA) and propyl gallate were evaluated using 1,1-Diphenyl-2-picrylhydrazyl radical (DPPH(•)), 2,2’-Azinobis-3- ethylbenzothiazoline-6-sulfonic acid radical (ABTS(+•)), Hydroxyl radical ((•)OH) and Superoxide radical (O2 (•-)) scavenging assays and reduction potential assay. By virtue of their hydrogen donating ability, phenolic compounds with multiple hydroxyl groups such as protocatechuic acid, pyrogallol, caffeic acid, gallic acid and propyl gallate exhibited higher free radical scavenging activity especially against DPPH(•) and O2 (•-). The hydroxylated cinnamates such as ferulic acid and caffeic acid were in general better scavengers than their benzoic acid counter parts such as vanillic acid and protocatechuic acid. All the phenolic compounds tested exhibited more than 85 % scavenging due to the high reactivity of the hydroxyl radical. Phenolic compounds with multiple hydroxyl groups also exhibited high redox potential. Exploring the radical scavenging and reducing properties of antioxidants especially those which are found naturally in plant sources are of great interest due to their protective roles in biological systems.

http://www.ncbi.nlm.nih.gov/pubmed/26344993

“The result showed that Propyl Gallate dose and time dependently decreased the growth of A549 cells ... In addition, DNA strand breaks have been observed through the comet assay technique.”

Drug Chemistry and Toxicology • July 2014

Geno- and cytotoxicity of propyl gallate food additive

Author information

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Abstract

Synthetic phenolic food additives, such as propyl 3,4,5-trihydroxybenzoate (propyl galate; PG), have been used as an antioxidant in the food industry to prevent oils from spoiling. Their toxicity is one of the challengeable issues resulting from the widespread usage of them in food-related industrials. In this study, we investigated the anticell proliferation effects of PG on A549 lung cancer cells. The result showed that PG dose and time dependently decreased the growth of A549 cells with an half-maximal inhibitory concentration of approximately 1 × 10(-3) and 5 × 10(-4)M of PG at 48 and 72 hours, respectively. In addition, DNA strand breaks have been observed through the comet assay technique. Also, morphology of 4’,6-diamidino-2-phenylindole (DAPI)-stained cells showed an obvious fragmentation in the chromatin and DNA rings within the nucleus of PG-treated cells, and, finally, flow cytometry analyses of the cells confirmed DAPI staining assay and determined early and late apoptosis in treated cells.

http://www.ncbi.nlm.nih.gov/pubmed/24160552

Molecular Biology Reports • April 2011

The enhancement of propyl gallate-induced HeLa cell death by MAPK inhibitors is accompanied by increasing ROS levels

Author information

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Abstract

Propyl gallate (PG) as a synthetic antioxidant exerts a variety of effects on tissue and cell functions. Here, we investigated the effects of MAPK (MEK, JNK and p38) inhibitors on PG-treated HeLa cells in relation to cell death, ROS and GSH levels. PG induced cell growth inhibition and apoptosis in HeLa cells, which was accompanied by the loss of mitochondrial membrane potential (MMP; Δßm). ROS levels were increased or decreased in PG-treated HeLa cells depending on the incubation times. PG also increased GSH depleted cell numbers in HeLa cells. All the MAPK inhibitors slightly enhanced cell growth inhibition, death and MMP (Δßm) loss, and increased ROS levels in PG-treated HeLa cells. However, MAPK inhibitors did not significantly affect GSH depletion in PG-treated cells. In conclusion, the enhanced effect of MAPK inhibitors on PG-induced HeLa cell death was accompanied by increasing ROS levels but the effect was not related to changes of GSH level.

http://www.ncbi.nlm.nih.gov/pubmed/21082265

“In conclusion, Propyl Gallate induced growth inhibition and death of endothelial cells, especially calf pulmonary artery endothelial cells ...”

Toxicology In Vitro • June 2010

Propyl gallate inhibits the growth of calf pulmonary arterial endothelial cells via glutathione depletion

Author information
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Abstract

Propyl gallate (PG) as a synthetic antioxidant exerts a variety of effects on tissue and cell functions. Here, we evaluated the effects of PG on the growth and death of endothelial cells (ECs), especially calf pulmonary artery endothelial cells (CPAEC) in relation to reactive oxygen species (ROS) and glutathione (GSH). PG dose-dependently inhibited the growth of CPAEC and human umbilical vein endothelial cells (HUVEC) at 24h. PG induced cell death in CPAEC, which was accompanied by the loss of mitochondrial membrane potential (MMP; DeltaPsi(m)). PG generally increased ROS level in CPAEC but not in HUVEC. PG also dose-dependently increased GSH depleted cells in both ECs. The treatment with antioxidant of N-acetyl-cysteine (NAC) or ascorbate acid (AA) prevented CPAEC growth inhibition and death by PG, which was accompanied by the attenuation of GSH depletion but not by the reduction of ROS level. In conclusion, PG induced growth inhibition and death of ECs, especially CPAEC via GSH depletion.

http://www.ncbi.nlm.nih.gov/pubmed/20159035

“Propyl gallate was found to act as an antagonist ... both ligands were active at nanomolar concentrations ... Some caution should be issued for the use of propyl gallate and 4-hexylresorcinol as food additives.”

Chemical Research And Toxicology • January 2009

Identification of xenoestrogens in food additives by an integrated in silico and in vitro approach

Author information
Amadasi A1, Mozzarelli A, Meda C, Maggi A, Cozzini P.
Department of Biochemistry and Molecular Biology
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Abstract

In the search for xenoestrogens within food additives, we have analyzed the Joint FAO-WHO expert committee database, containing 1500 compounds, using an integrated in silico and in vitro approach. This analysis identified 31 potential estrogen receptor alpha ligands that were reduced to 13 upon applying a stringent filter based on ligand volume and binding mode. Among the 13 potential xenoestrogens, four were already known to exhibit an estrogenic activity, and the other nine were assayed in vitro, determining the binding affinity to the receptor and biological effects. Propyl gallate was found to act as an antagonist, and 4-hexylresorcinol was found to act as a potent transactivator; both ligands were active at nanomolar concentrations, as predicted by the in silico analysis. Some caution should be issued for the use of propyl gallate and 4-hexylresorcinol as food additives.

Full text, graphs, charts and 102 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2758355/

“Propyl gallate and its metabolite, gallic acid, are widely used as antioxidants in the food industry, but they have been shown to exhibit liver toxicity and enhance carcinogenesis.”

Mutation Research • February 2008

Gallic acid, a metabolite of the antioxidant propyl gallate, inhibits gap junctional intercellular communication via phosphorylation of connexin 43 and extracellular-signal-regulated kinase1/2 in rat liver epithelial cells

Author information

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Abstract

Propyl gallate and its metabolite, gallic acid, are widely used as antioxidants in the food industry, but they have been shown to exhibit liver toxicity and enhance carcinogenesis. In the present study, we investigated the possible undesirable effects of propyl gallate and gallic acid on gap junctional intercellular communication (GJIC), inhibition of which is closely linked to carcinogenesis. Gallic acid and propyl gallate exhibited dose-dependent free-radical-scavenging activities as determined by 1,1-diphenyl-2-picrylhydrazyl- or 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)-radical-scavenging assays, and the free-radical-scavenging activity of gallic acid was stronger than that of propyl gallate. However, using WB-F344 rat liver epithelial cells, gallic acid inhibited GJIC in a dose-dependent manner, while propyl gallate had no significant effect compared with untreated controls. The gallic-acid-induced inhibition of GJIC was reversible, with a recovery of nearly 65% after 120 min. Gallic acid induced the phosphorylation of connexin 43 (Cx43) and phosphorylation of extracellular-signal-regulated kinase1/2 (ERK1/2). The gallic-acid-induced inhibition of GJIC was attenuated by treatment with mitogen-activated protein kinase kinase inhibitors (U0126 and PD098059). U0126 blocked the gallic-acid-induced phosphorylation of Cx43 and ERK1/2, indicating that the gallic-acid-induced inhibition of GJIC is mediated by phosphorylation of Cx43 via activation of ERK1/2. In addition, gallic-acid-induced inhibition of GJIC was protected by ascorbic acid and quercetin, which might represent a simple example of the different effects of natural antioxidants in carcinogenesis.

http://www.ncbi.nlm.nih.gov/pubmed/18054051

“This study shows the value of gene expression profiling in food toxicology in terms of generating novel hypotheses on the mechanisms of action of food additives in relation to pathology.”

Food And Chemical Toxicology • August 2008

Transcriptome analysis provides new insights into liver changes induced in the rat upon dietary administration of the food additives butylated hydroxytoluene, curcumin, propyl gallate and thiabendazole

Author information

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Abstract

Transcriptomics was performed to gain insight into mechanisms of food additives butylated hydroxytoluene (BHT), curcumin (CC), propyl gallate (PG), and thiabendazole (TB), additives for which interactions in the liver can not be excluded. Additives were administered in diets for 28 days to Sprague-Dawley rats and cDNA microarray experiments were performed on hepatic RNA. BHT induced changes in the expression of 10 genes, including phase I (CYP2B1/2; CYP3A9; CYP2C6) and phase II metabolism (GST mu2). The CYP2B1/2 and GST expression findings were confirmed by real time RT-PCR, western blotting, and increased GST activity towards DCNB. CC altered the expression of 12 genes. Three out of these were related to peroxisomes (phytanoyl-CoA dioxygenase, enoyl-CoA hydratase; CYP4A3). Increased cyanide insensitive palmitoyl-CoA oxidation was observed, suggesting that CC is a weak peroxisome proliferator. TB changed the expression of 12 genes, including CYP1A2. In line, CYP1A2 protein expression was increased. The expression level of five genes, associated with p53 was found to change upon TB treatment, including p53 itself, GADD45alpha, DN-7, protein kinase C beta and serum albumin. These array experiments led to the novel finding that TB is capable of inducing p53 at the protein level, at least at the highest dose levels employed above the current NOAEL. The expression of eight genes changed upon PG administration. This study shows the value of gene expression profiling in food toxicology in terms of generating novel hypotheses on the mechanisms of action of food additives in relation to pathology.

http://www.ncbi.nlm.nih.gov/pubmed/18539377

“According to the results, propyl gallate should be classified as toxic to aquatic organisms.”

Water Research • June 2007

Ecotoxicological effects of the antioxidant additive propyl gallate in five aquatic systems

Author information
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National Institute of Toxicology and Forensic Sciences, Av. Dr Fedriani s/n, 41009 Seville, Spain

Abstract

Propyl gallate is an antioxidant widely used in foods, cosmetics and pharmaceuticals. The occurrence and fate of additives in the aquatic environment is an emerging issue in environmental chemistry. To date, there is little available information about the adverse effects of propyl gallate on aquatic organisms. Therefore, the toxic effects were investigated, using five model systems from four trophic levels. The most sensitive system was the hepatoma fish cell line PLHC-1 according to total protein content, with an EC(50) of 10 microM and a NOAEL of 1 microM at 72 h, followed by the immobilization of Daphnia magna, the inhibition of bioluminescence of Vibrio fischeri, the salmonid fish cell line RTG-2 and the inhibition of the growth of Chlorella vulgaris. Although protein content, neutral red uptake, methylthiazol metabolization and acetylcholinesterase activity were reduced in PLHC-1 cells, stimulations were observed for lysosomal function, succinate dehydrogenase, glucose-6-phosphate dehydrogenase and ethoxyresorufin-O-deethylase activities. No changes were observed in metallothionein levels. The main morphological observations were the loss of cells and the induction of cell death mainly by necrosis but also by apoptosis. The protective and toxic effects of propyl gallate were evaluated. General antioxidants and calcium chelators did not modify the toxicity of propyl gallate, but an iron-dependent lipid peroxidation inhibitor gave 22% protection. The results also suggest that propyl gallate cytotoxicity is dependent on glutathione levels, which were modulated by malic acid diethyl ester and 2-oxothiazolidine-4-carboxylic acid. According to the results, propyl gallate should be classified as toxic to aquatic organisms.

http://www.ncbi.nlm.nih.gov/pubmed/17382989

“Propyl Gallate was found to have a strong inhibitory effect on Benzene-induced mutations.”

Food Chemistry And Toxicology • October 2007

Effects of various plant polyphenols on bladder carcinogen benzidine-induced mutagenicity

Author information
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Abstract

Benzidine (Bz), a human bladder carcinogen, was strongly mutagenic to Salmonella TA102 tester strain in the Ames Salmonella microsome/mutagenicity assay in the presence of rat liver S9 mix. Various non-mutagenic plant polyphenols were included in the assay to test their inhibitory effects on the Bz-induced mutations. Coumestrol, ellagic acid (EA), (-)-epicatechin (EC), (-)-epichatechingallate (ECG), gallic acid (GA), (-)-gallocatechin (GC), plumbagin, propyl gallate (PG), taxifolin, and 2,2’,4’-trihydroxychalcone were found to have a strong inhibitory effect on Bz-induced mutations. (-)-Epigallo-catechingallate (EGCG), fisetin, (-)-gallocatechingallate (GCG), and piceatannol were moderately inhibitory to the mutations; whereas, (-)-catechin, (-)-catechingallate (CG), and reseveratrol were weakly inhibitory to the mutations. (-)-Epigallocatechin (EGC) and 7,3’,4’-trihydroxy isoflavon were not inhibitory to the Bz-induced mutations. Isoliquirtigenin, quercetin dihydrate, and rhein were found to be mutagenic in tester strain TA102. Benzidine mediated lipid peroxidation was conducted employing the thiobarbituric acid reactive substances (TBARS) assay using linoleic acid as a substrate. In the presence of rat liver S9 mix, Bz could cause lipid peroxidation as an outcome of production of oxygen free radicals. Incorporation of the above mentioned non-mutagenic plant polyphenols significantly inhibited benzidine mediated lipid peroxidation in a time dependent manner. These polyphenols also effectively reduced the iron mediated lipid peroxidation. Thus, it is concluded that the inhibition of oxidative mutagenicity of Bz by plant polyphenols could be due to an inhibitory effect of plant polyphenols on the bioactivating enzymes such as cytochrome P-450 and peroxidase and the chelation of iron present in the cytochrome P-450 in the S9 mix. Thus, these plant polyphenols play a significant inhibitory role on Bz-induced mutagenicity.

http://www.ncbi.nlm.nih.gov/pubmed/17560706

“... an example is shown in which gene expression profiling together with conventional biochemistry led to the discovery of novel markers for the hepatic effects of the food additives butylated hydroxytoluene, curcumin, propyl gallate and thiabendazole.”

Toxicology And Applied Pharmacology • September 2005

Toxicogenomics concepts and applications to study hepatic effects of food additives and chemicals

Author information
Stierum R1, Heijne W, Kienhuis A, van Ommen B, Groten J.
Physiological Sciences Department, TNO Quality of Life, Zeist, The Netherlands

Abstract

Transcriptomics, proteomics and metabolomics are genomics technologies with great potential in toxicological sciences. Toxicogenomics involves the integration of conventional toxicological examinations with gene, protein or metabolite expression profiles. An overview together with selected examples of the possibilities of genomics in toxicology is given. The expectations raised by toxicogenomics are earlier and more sensitive detection of toxicity. Furthermore, toxicogenomics will provide a better understanding of the mechanism of toxicity and may facilitate the prediction of toxicity of unknown compounds. Mechanism-based markers of toxicity can be discovered and improved interspecies and in vitro-in vivo extrapolations will drive model developments in toxicology. Toxicological assessment of chemical mixtures will benefit from the new molecular biological tools. In our laboratory, toxicogenomics is predominantly applied for elucidation of mechanisms of action and discovery of novel pathway-supported mechanism-based markers of liver toxicity. In addition, we aim to integrate transcriptome, proteome and metabolome data, supported by bioinformatics to develop a systems biology approach for toxicology. Transcriptomics and proteomics studies on bromobenzene-mediated hepatotoxicity in the rat are discussed. Finally, an example is shown in which gene expression profiling together with conventional biochemistry led to the discovery of novel markers for the hepatic effects of the food additives butylated hydroxytoluene, curcumin, propyl gallate and thiabendazole.

http://www.ncbi.nlm.nih.gov/pubmed/16139318

Toxicology And Applied Pharmacology • December 2005

Relationship of CD86 surface marker expression and cytotoxicity on dendritic cells exposed to chemical allergen

Author information

Hulette BC1, Ryan CA, Gildea LA, Gerberick GF.
The Procter and Gamble Company, Miami Valley Laboratories, PO Box 538707, Cincinnati, OH 45253-8707, USA

Abstract

Human peripheral blood-derived dendritic cells (DC) respond to a variety of chemical allergens by up-regulating expression of the co-stimulatory molecule CD86. It has been postulated that this measure might provide the basis for an in vitro alternative approach for the identification of skin sensitizing chemicals. We recently reported that DC, exposed in culture to the highest non-cytotoxic concentrations of various chemical allergens, displayed marginal up-regulation of membrane CD86 expression; the interpretation being that such changes were insufficiently sensitive for the purposes of hazard identification. For the work presented here, immature DC were derived from human monocytes and treated with the chemical allergens 2,4-dinitrobenzenesulfonic acid (DNBS), nickel sulfate (NiSO4), p-phenylenediamine (PPD), Bandrowski's base (BB), hydroquinone (HQ) and propyl gallate (PG) for 48 h at concentrations which induced both no to slight to moderate cytotoxicity. For comparison, DC were treated with the irritants sodium dodecyl sulfate (SDS), benzoic acid (BA), and benzalkonium chloride (BZC) at concentrations resulting in comparable levels of cytotoxicity. CD86 expression, as measured by flow cytometry, was consistently up-regulated (ranging from 162 to 386% control) on DC treated with concentrations of chemical allergens that induced approximately 10-15% cytotoxicity. The irritants BA and BZC did not induce up-regulation of CD86 expression when tested at concentrations that induced similar levels of cytotoxicity. SDS, however, up-regulated CD86 expression to 125-138% of control in 2/4 preparations when tested at concentrations which induced similar toxicity. Our results confirm that chemical allergens up-regulate CD86 expression on blood-derived DC and illustrate further that up-regulation of CD86 surface marker expression is more robust when DC are treated with concentrations of chemical allergen that induce slight to moderate cytotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/15885735

“In conclusion, PG in the presence or absence of (1.5-9%), gallic acid can induce sister-chromatid exchanges, chromosomal aberrations, and endoreduplications, and the oxides, metabolites and oxygen-free radicals generated during the treatment are partly responsible for these effects.”

Mutation Research • November 2001

Cytogenetic effects of propyl gallate in CHO-K1 cells

Author information

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Abstract

We investigated whether propyl gallate (PG) can induce sister-chromatid exchanges (SCEs) and chromosomal aberrations (CAs) in CHO-K1 cells. In the absence of an exogeneous metabolizing system, treatments with 0.25-1.5mM PG in plugged flasks for 3h resulted in increases in SCEs, CAs, and endoreduplications (ERDs), which were followed by an increase in the percentage of cells showing cell-cycle delay. At the end of the treatment, a decrease in PG concentration and production of PG dimer and ellagic acid (EA) in the medium were detected, indicating that PG had autoxidized. EA, an oxide of PG, was not genotoxic even at 0.3mM, the maximum concentration soluble in the medium. Several oxygen radical scavengers (superoxide dismutase (SOD), catalase, glutathione and o-phenanthroline (OP)) and an inhibitor of catalase activity (3-amino-1,2,4-triazole (AT)), did not significantly influence PG genotoxicity. When PG autoxidation was suppressed by low pH (6.8) or a 5% CO(2) atmosphere, cell-cycle delay intensified and induction of SCEs and CAs occurred even at the lowest PG dose (0.1mM). When PG (0.5mM) was assayed in the presence of S9 (1.5-9%), gallic acid (GA), a metabolite of PG, was generated in direct proportion to the S9 concentration, while cell-cycle delay and genotoxic effects varied inversely with S9 concentration at the levels over 3%. GA also autoxidized and at >or=0.5mM it induced SCEs. Both catalase and AT suppressed the induction of SCEs by GA or inhibited cell proliferation, indicating that H(2)O(2) participated in the effects. In conclusion, PG in the presence or absence of S9 can induce SCEs, CAs, and ERDs, and the oxides, metabolites and oxygen-free radicals generated during the treatment are partly responsible for these effects.

http://www.ncbi.nlm.nih.gov/pubmed/11673077

“Our results demonstrate that the antioxidative and cytoprotective properties of propyl gallate may change to prooxidative, cytotoxic and genotoxic properties in the presence of Copper.”

Free Radical Biology And Medicine • April 1998

DNA strand break induction and enhanced cytotoxicity of propyl gallate in the presence of copper(II)

Author information

Jacobi H1, Eicke B, Witte I.
Carl von Ossietzky Universität Oldenburg, Germany

Abstract

The antioxidant propyl gallate (PG) induced single strand breaks in PM2 DNA at concentrations higher than 0.25 microM when it was combined with copper concentrations at 5 microM and above. In combination with 100 microM CuCl2, extensive double strand breakage was also observed. Neither PG alone nor CuCl2 showed any strand breaking properties. DNA strand breakage was inhibited by addition of catalase or the Cu(I) chelator neocuproine, indicating the involvement of H2O2 and a Cu(II)/Cu(I) redox cycle in the DNA damage. DNA damage of PG/Cu(II) was also observed in human fibroblasts. Using the alkaline elution technique concentrations of 0.15-0.5 mM PG induced DNA strand breaks in combination with 2.5 mM CuCl2, while the single substances did not show any effect. At these concentrations cell viability measured by the MTT assay was not reduced by more than 10%; however, cell growth was inhibited by PG in combination with Cu(II). This growth inhibition was apparently due to the DNA damage incurred by PG/Cu(II). The synergistic interaction between PG and Cu(II) is probably caused by a redox reaction between both compounds, whereby reactive species such as ROS are formed, which are responsible for the observed genotoxic and cytotoxic effects. Our results demonstrate that the antioxidative and cytoprotective properties of propyl gallate may change to prooxidative, cytotoxic and genotoxic properties in the presence of Cu(II).

http://www.ncbi.nlm.nih.gov/pubmed/9607607

“The present data demonstrate that copper and iron ions modify the cytotoxic activity of these antioxidants differently and their radical intensity is not the sole determinant of cytotoxic activity.”

Anticancer Research • May 1997

Effect of copper and iron ions on cytotoxicity induced by ascorbate, gallate and caffeate

Author information

Satoh K1, Sakagami H.
Analysis Center, School of Pharmaceutical Sciences, Showa University, Tokyo, Japan

Abstract

Four antioxidants, sodium ascorbate, gallic acid, n-propyl gallate and caffeic acid, induced apoptotic cell death in human promyelocytic leukemic HL-60 cells. The effects of all these compounds were enhanced by CuCl2 or deferoxamine mesylate, an iron chelator, but were reduced by FeCl3. ESR spectroscopy showed that both CuCl2 and FeCl3 enhanced the ascorbyl radical intensity, but reduced the gallate and caffeate radical intensity. The present data demonstrate that copper and iron ions modify the cytotoxic activity of these antioxidants differently and their radical intensity is not the sole determinant of cytotoxic activity.

http://www.ncbi.nlm.nih.gov/pubmed/9216684

“Pretreatment of the cells with alpha-tocopherol [vitamin E] significantly increased the resistancy against the cytotoxic action of UV irradiation and antioxidants such as sodium ascorbate, gallic acid, n-propyl gallate and caffeic acid.”

Anticancer Research • May 1997

Effect of alpha-tocopherol on cytotoxicity induced by UV irradiation and antioxidants

Author information

Sakagami H1, Satoh K, Makino Y, Kojima T, Takeda M.
Department of Biochemistry, School of Medicine, Showa University, Tokyo, Japan

Abstract

The addition of DL-alpha-tocopherol (vitamin E) at the time of UV irradiation only marginally protects cells from UV-induced cytotoxicity. However, a protective effect of alpha-tocopherol emerged when it was added to the cells before UV irradiation, alpha-Tocopherol was progressively and dose-dependently incorporated into the cells. Washout experiments showed that the intracellular concentration of alpha-tocopherol decreased with an approximate half-life of 14-20 hours, due to the release from the cells and dilution by cell proliferation. Pretreatment of the cells with alpha-tocopherol significantly increased the resistancy against the cytotoxic action of UV irradiation and antioxidants such as sodium ascorbate, gallic acid, n-propyl gallate and caffeic acid. ESR spectroscopy showed that alpha-tocopherol enhanced the ascorbyl radical intensity, whereas it reduced caffeic acid radical intensity, without affecting the radical intensity of gallic acid and n-propyl gallate. Both control and treated cell lysates scavenged superoxide anion (generated by xanthine-xanthine oxidase reaction) and hydroxyl radical (generated by Fenton reaction) to a comparable extent. The present study suggests that the protective effect of alpha-tocopherol might be derived from its incorporation into the cell membranes rather than its scavenging activity.

http://www.ncbi.nlm.nih.gov/pubmed/9216667

“These results suggest that when the concentration of propyl gallate is decreased, the effects of propyl gallate on hepatocytes change from acute necrotic to apoptotic mode, and that the onset of DNA fragmentation is associated with glutathione depletion.”

Archives In Toxicology • December 1997

Propyl gallate-induced DNA fragmentation in isolated rat hepatocytes

Author information

Nakagawa Y1, Moldéus P, Moore G.
Department of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, Japan

Abstract

Incubation of isolated rat hepatocytes with propyl gallate (PG) at concentrations of > or = 1 mM induced cell killing, whereas PG at < or = 0.5 mM did not cause cell death during a 3-h incubation. PG at > or = 0.5 mM elicited the ladder formation of soluble low-molecular weight DNA fragments with integer multiples of approximately 180 bp and specific nuclear DNA cleavages detected cytopathologically by labeling of a digoxigenin-nucleotide complex to new 3’-OH ends. Both of these PG-induced changes observed in hepatocytes are characteristic features of apoptosis. In contrast, the pretreatment of N-acetylcysteine (4 mM), a precursor of intracellular glutathione (GSH) and antioxidant, prevented PG (0.5 mM)-induced formation of soluble DNA fragments and loss of cellular GSH, ATP, and formation of blebbing. These results suggest that when the concentration of PG is decreased, the effects of PG on hepatocytes change from acute necrotic to apoptotic mode, and that the onset of DNA fragmentation is associated with GSH depletion.

http://www.ncbi.nlm.nih.gov/pubmed/9458188

“These results indicate that the onset of cytotoxicity caused by propyl gallate may depend on the intracellular energy status and that mitochondria are critical target for the compound. In addition, the toxicity caused by the inhibition of mitochondrial Adenosine Triphosphate synthesis is related to the concentration of propyl gallate remaining in cell suspensions.”

Toxicology • December 1996

Relationship between mitochondrial dysfunction and toxicity of propyl gallate in isolated rat hepatocytes

Author information
Nakagawa Y1, Moldéus P, Moore GA.
Department of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, Japan

Abstract

The relationship between cytotoxicity and mitochondrial dysfunction caused by propyl gallate (PG) has been studied in hepatocytes freshly prepared from fasted rats. Hepatocytes isolated from fasted (18 h) rats were significantly more susceptible to the toxicity of PG than hepatocytes from fed rats. The addition of fructose (15 mM), an alternative carbohydrate source, to hepatocyte suspensions resulted in the prevention of PG (1 mM)-induced cell killing accompanied by decrease in intracellular ATP loss during a 3 h-incubation period. Despite this, fructose did not completely prevent an abrupt loss of intracellular glutathione caused by PG, but effectively inhibited the loss of protein thiol levels. Fructose elicited a concentration (0.5-20mM)-dependent protection against the cytotoxicity of 1.5 mM PG. The incubation of hepatocytes with sodium azide (4 mM), an inhibitor of oxidative phosphorylation, enhanced the toxicity induced by PG (1 mM), but coincubation with fructose delayed the onset of toxicity. Neither azide alone nor fructose plus azide did affect the cell viability during the incubation period. Furthermore, the addition of 2 mM salicylamide, nontoxic to hepatocytes during the incubation period, enhanced PG (1 mM)-induced cytotoxicity and decreased the loss of free PG. These results indicate that the onset of cytotoxicity caused by PG may depend on the intracellular energy status and that mitochondria are critical target for the compound. In addition, the toxicity caused by the inhibition of mitochondrial ATP synthesis is related to the concentration of PG remaining in cell suspensions.

http://www.ncbi.nlm.nih.gov/pubmed/8947612

“These results indicate (a) that propyl gallate-induced hepatotoxicity is mediated by the parent compound and not its metabolites, (b) that toxicity is associated with Adenosine Triphosphate depletion apparently independently of cellular thiol depletion, and (c) that mitochondria may represent critical targets of propyl gallate-induced cytotoxicity.”

Molecular Pharmacology • May 1995

Metabolism and cytotoxicity of propyl gallate in isolated rat hepatocytes: effects of a thiol reductant and an esterase inhibitor

Author information

Nakagawa Y1, Nakajima K, Tayama S, Moldéus P.
Department of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, Japan

Abstract

The relationship between the metabolism and the cytotoxic effects of propyl gallate (PG) has been studied in freshly isolated rat hepatocytes. Addition of PG (0.5-2.0 mM) to the hepatocytes elicited concentration-dependent cell death, accompanied by decreases in intracellular ATP, adenine nucleotide pools, glutathione, and protein thiols. The rapid loss of ATP preceded the onset of cell death. PG in the hepatocyte suspensions was converted to gallic acid, 4-O-methyl-gallic acid, and other minor products over time. In addition, PG was converted to a dimer [dipropyl-4,4’,5,5’,6,6’-hexahydroxydiphenate (PG-dimer)] and ellagic acid via autooxidation. In comparisons of the toxic effects of PG and its metabolites at concentrations of 2 mM, the parent compound PG was the most toxic. Pretreatment of hepatocytes with diazinon (100 microM), an esterase inhibitor, enhanced PG-induced cytotoxicity. This was accompanied by delay of PG loss and inhibition of gallic acid formation. The cytotoxicity of PG was also enhanced by addition of the thiol reductant dithiothreitol (4 mM), although intracellular levels of glutathione and protein thiols were maintained during the incubation period. Dithiothreitol did not affect the hydrolysis of PG to gallic acid by esterases but did delay the conversion of PG and prevented the formation of PG-dimer. In isolated hepatic mitochondria, PG elicited a concentration-dependent increase in the rate of state 4 oxygen consumption, indicating an uncoupling effect. In contrast, PG-dimer inhibited the rate of state 3 oxygen consumption. Based on the respiratory control index, the order of potency for impairment of mitochondria was PG > PG-dimer > gallic acid = 4-O-methyl-gallic acid = ellagic acid - propyl alcohol. These results indicate (a) that PG-induced hepatotoxicity is mediated by the parent compound and not its metabolites, (b) that toxicity is associated with ATP depletion apparently independently of cellular thiol depletion, and (c) that mitochondria may represent critical targets of PG-induced cytotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/7746268

“These results indicate that propyl gallate and related gallates are toxic to hepatocytes and that the acute cytotoxicity may be due to mitochondrial dysfunction.”

Archives In Toxicology • December 1995

Cytotoxicity of propyl gallate and related compounds in rat hepatocytes

Author information

Nakagawa Y1, Tayama S.
Tokyo Metropolitan Research Laboratory of Public Health, Japan

Abstract

The cytotoxic effects of propyl gallate (PG), its related gallates and gallic acid have been studied in freshly isolated rat hepatocytes. Addition of PG (0.5-2.0 mM) to hepatocyte suspension elicited concentration-dependent cell death accompanied by losses of intracellular ATP, adenine nucleotide pools, glutathione (GSH) and protein thiols. The rapid loss of intracellular ATP preceded the onset of cell death caused by PG. In the comparative toxic effects of PG and related gallates at concentration of 1 mM, octyl gallate (OG), dodecyl gallate (DG) and butyl gallate (BG) elicited an abrupt depletion of ATP, followed by an acute cell death. These gallates were more toxic than PG; the toxic effects of PG were similar to those of methyl gallate (MG) and ethyl gallate (EG). In mitochondria isolated from rat liver, PG caused a concentration-dependent increase in the rate of state 4 oxygen consumption, indicating an uncoupling effect. The rate of state 3 oxygen consumption was inhibited by OG and DG. According to the respiratory control index, the order of impairment potency to mitochondria was OG > BG, DG > PG > EG, MG > gallic acid. These results indicate that PG and related gallates are toxic to hepatocytes and that the acute cytotoxicity may be due to mitochondrial dysfunction.

http://www.ncbi.nlm.nih.gov/pubmed/7717878

“TBHQ significantly elevated the incidences of esophageal papillary or nodular (PN) hyperplasias and papillomas, as well as forestomach papillomas, but significantly decreased the multiplicity of colon adenocarcinomas. Propyl Gallate was only effective in reducing the multiplicity of kidney atypical tubules. BHT enhanced the development of thyroid hyperplasias, but strongly reduced the incidence and multiplicity of colon adenocarcinomas. This compound was also associated with lowered incidence and multiplicity of renal cell tumors. None of the agents studied was unequivocal in exerting either positive or negative influence.”

Carcinogenesis • November 1993

Modification of carcinogenesis by alpha-tocopherol, t-butylhydroquinone, propyl gallate and butylated hydroxytoluene in a rat multi-organ carcinogenesis model

Hirose M1, Yada H, Hakoi K, Takahashi S, Ito N.
First Department of Pathology, Nagoya City University, Medical School, Japan

Abstract

Effects of the dietary antioxidants alpha-tocopherol (alpha-Toc), t-butylhydroquinone (TBHQ), propyl gallate (PG) and butylated hydroxytoluene (BHT) were examined using a multi-organ carcinogenesis model. Groups of 20 F344 male rats were treated with a single intragastric administration of 100 mg/kg body weight N-methyl-N’-nitro-N-nitroso-guanidine, a single intragastric administration of 750 mg/kg body weight N-ethyl-N-hydroxyethylnitrosamine, two subcutaneous injections of 0.5 mg/kg body weight N-methylbenzyl-nitrosamine and four subcutaneous injections of 40 mg/kg body weight 1,2-dimethylhydrazine. At the same time the rats were given 0.1% N-dibutylnitrosamine for 4 weeks and then 0.1% 2,2’-dihydroxy-di-n-propylnitrosamine for 2 weeks in the drinking water, for a total carcinogen exposure period of 6 weeks. Starting 3 days thereafter the rats received 1% alpha-Toc, 1% TBHQ, 1% PG or 0.7% BHT in the diet, or basal diet alone. Further groups of 10-15 animals each were treated with antioxidant alone or basal diet alone as controls. Surviving animals were killed at the end of week 36. Histopathological examination showed that alpha-Toc increased the incidence of glandular stomach atypical foci but reduced the incidence and multiplicity of kidney atypical tubules. TBHQ significantly elevated the incidences of esophageal papillary or nodular (PN) hyperplasias and papillomas, as well as forestomach papillomas, but significantly decreased the multiplicity of colon adenocarcinomas. PG was only effective in reducing the multiplicity of kidney atypical tubules. BHT enhanced the development of thyroid hyperplasias, but strongly reduced the incidence and multiplicity of colon adenocarcinomas. This compound was also associated with lowered incidence and multiplicity of renal cell tumors. None of the agents studied was unequivocal in exerting either positive or negative influence.

http://www.ncbi.nlm.nih.gov/pubmed/8242867

“Histological examination revealed significantly increased incidences of hyperplasia in the groups given BHA together with ... Propyl Gallate.”

Carcinogenesis • November 1987

Enhancement of BHA-induced proliferative rat forestomach lesion development by simultaneous treatment with other antioxidants

Author information

Hirose M1, Masuda A, Tsuda H, Uwagawa S, Ito N.
First Department of Pathology, Nagoya City University Medical School, Japan

Abstract

Synergistic effects of butylated hydroxyanisole (BHA) and other antioxidants on induction of rat forestomach lesions were investigated. Groups of F344 male rats were treated with 1% BHA plus 0.7% butylated hydroxytoluene (BHT), 1% BHA plus 1% propyl gallate (PG), 1% BHA plus 1% sodium L-ascorbate (SA), 1% BHA plus 1% DL-alpha-tocopherol (alpha-TP), 0.4% BHT plus 0.4% BHA plus 0.4% PG plus 0.4% SA plus 0.4% alpha-TP, 1% BHA or 2% BHA. Further groups of 10 rats each received antioxidants without BHA as controls. Histological examination revealed significantly increased incidences of hyperplasia in the groups given BHA together with SA or PG at the prefundic region or at the mid region respectively. The forestomach changes induced by BHA together with SA were equal to those induced by 2% BHA. On the other hand, simultaneous treatment with BHA and PG or alpha-TP reduced the incidence of hyperplasia at the prefundic region. It is concluded that mixed treatment with BHA and other antioxidants exerted enhancing or inhibitory effects on the induction of hyperplasia at different sites of the forestomach epithelium.

http://www.ncbi.nlm.nih.gov/pubmed/3664967

“propyl gallate should be classified as toxic.”

Toxicology And Pathology • December 1986

Modifying effects of antioxidants on chemical carcinogenesis

Ito N, Hirose M, Fukushima S, Tsuda H, Tatematsu M, Asamoto M.

Abstract

Studies were made on the carcinogenic activity of butylated hydroxyanisole (BHA) in rats, mice, and hamsters and the effect of the antioxidants BHA, butylated hydroxytoluene (BHT), ethoxyquin (EQ), sodium L-ascorbate (SA), ascorbic acid (AA), sodium erythorbate (SE), propyl gallate (PG), and alpha-tocopherol, on two-stage chemical carcinogenesis in rats initiated with N-methyl-N’-nitro-N-nitrosoguanidine (MNNG), 1,2-dimethylhydrazine (DMH), diethylnitrosamine (DEN), 7,12-dimethylbenz(a)anthracene (DMBA), N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), N-ethyl-N-hydroxyethylnitrosamine (EHEN), or N-methylnitrosourea (MNU). BHA clearly induced squamous cell carcinomas in both the rat and hamster forestomach. The tumorigenic action of crude BHA on the forestomach is largely due to 3-tert-BHA. In two-stage chemical carcinogenesis, BHA promoted MNNG or MNU-initiated forestomach and BBN- or MNU-initiated urinary bladder carcinogenesis and inhibited DEN- or EHEN-initiated liver and DMBA-initiated mammary carcinogenesis. BHT demonstrated promotion potential for urinary bladder and MNU-initiated thyroid carcinogenesis and inhibited DMBA-initiated ear duct carcinogenesis. EQ promoted EHEN-initiated kidney carcinogenesis and inhibited DMBA-initiated mammary and EHEN-initiated liver carcinogenesis. SA promoted forestomach and urinary bladder carcinogenesis and SE likewise enhanced urinary bladder carcinogenesis. alpha-Tocopherol inhibited ear duct carcinogenesis. No effects of any of the antioxidants on glandular stomach carcinogenesis were found. The results clearly demonstrated that antioxidants have different effects (promoting or inhibitory influences) depending on the organ studied and suggest the importance of a whole body approach to their investigation.

Full text, PDF, graphs, charts and 38 references

http://tpx.sagepub.com/content/14/3/315.full.pdf

Clinical Toxicology • October 1979

Infantile methemoglobinemia caused by food additives

By M. Nitzan, B. Volovitz and E. Topper

Abstract

"A small outbreak of toxic methemoglobinemia occurred among infants in a pediatric ward. Investigation revealed that the most likely source of toxicity was an approved fat preservative which had been added to a soybean infant formula by the manufacturer. This fat preservative contained three phenolic compounds having highly effective antioxygenic properties (butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and propyl gallate). The outbreak ceased when the offending agents were eliminated from the food preparation. It is emphasized that the approval of chemicals for use in the food industry through toxicity studies does not necessarily guarantee against the hazards of toxicity, especially during infancy."

http://www.ncbi.nlm.nih.gov/pubmed/509890

CHAPTER THIRTEEN

Providone or Povidone aka Betadine

The Peer Review

Povidone-iodine is a drug and whether you call it Providone or Betadine, it's a drug. It happens to have food additive qualities but it's still a drug. Povidone-iodine (PVP-I), brand name Wokadine, Pyodine, and Betadine is a stable chemical complex of polyvinylpyrrolidone (povidone, PVP) and elemental iodine. It contains from 9.0% to 12.0% available iodine, calculated on a dry basis.

This unique complex was discovered in 1955 at the Industrial Toxicology Laboratories in Philadelphia by H. A. Shelanski and M. V. Shelanski. They carried out tests in vitro to demonstrate anti-bacterial activity, and found that the complex was less toxic in mice than tincture of iodine.

Human clinical trials showed the product to be superior to other iodine formulations. Betadine was immediately marketed, and has since become the universally preferred iodine antiseptic. Betadine is only sold for the purpose of healing wounds, and not as an oral sore throat gargle, as widely thought. It's on the WHO Model List of Essential Medicines, the most important products needed in a basic health system.

Povidone-iodine is a broad spectrum antiseptic for topical application in the treatment and prevention of infection in wounds. It may be used in first aid for minor cuts, grazes, burns, abrasions and blisters.

Following the discovery of iodine by Bernard Courtois in 1811, it's been broadly used for the prevention and treatment of skin infections, as well as the treatment of wounds. Iodine has been recognized as an effective broad-spectrum bactericide, and is also effective against yeasts, molds, fungi, viruses, and protozoans. Drawbacks to its use in the form of aqueous solutions include irritation at the site of application, toxicity, and the staining of surrounding tissues. These deficiencies were overcome by the discovery and use of PVP-I, in which the iodine is carried in a complexed form and the concentration of free iodine is very low. The product thus serves as an iodophor.

In addition, it has been demonstrated that bacteria do not develop resistance to PVP-I, and the sensitization rate to the product is only 0.7% of the population. PVP-I has found broad application in medicine as a surgical scrub; for pre- and post-operative skin cleansing; for the treatment and prevention of infections in wounds, ulcers, cuts and burns; for the treatment of infections in decubitus ulcers and stasis ulcers; in gynecology for vaginitis associated with candidal, trichomonal or mixed infections. For these purposes PVP-I has been formulated at concentrations of 7.5–10.0% in solution, spray, surgical scrub, ointment, and swab dosage forms. It's available without a prescription under the generic name povidone-iodine or the brand name Betadine.

Povidone-iodine has found application in the field of nanomaterials. A wound-healing application has been developed which employs a mat of single wall carbon nanotubes (SWNTs) coated in a monolayer of povidone-iodine.

Povidone is a relatively new food additive used just in the last few years under the GRAS cover and there's very little data on it's effect in the human body as a food component. Nevertheless, here are the best available reports on the antiseptic and now food additive, Povidone, so that you can become familiar with an emerging new food drug.

Cochrane Database Of Systematic Reviews • April 2015

Preoperative skin antiseptics for preventing surgical wound infections after clean surgery

Author information

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Abstract

BACKGROUND

Surgical site infection rates in the month following clean surgery vary from 0.6% (knee prosthesis) to 5% (limb amputation). Due to the large number of clean surgical procedures conducted annually the costs of these surgical site infections (SSIs) can be considerable in financial and social terms. Preoperative skin antisepsis using antiseptics is performed to reduce the risk of SSIs by removing soil and transient organisms from the skin where a surgical incision will be made. Antiseptics are thought to be toxic to bacteria and therefore aid their mechanical removal. The effectiveness of preoperative skin preparation is thought to be dependent on both the antiseptic used and the method of application, however, it is unclear whether preoperative skin antisepsis actually reduces postoperative wound infection, and, if so, which antiseptic is most effective.

OBJECTIVES

To determine whether preoperative skin antisepsis immediately prior to surgical incision for clean surgery prevents SSI and to determine the comparative effectiveness of alternative antiseptics.

SEARCH METHODS

For this third update we searched just the Cochrane Wounds Group Specialised Register (searched 27 January 2015); The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2014, Issue 12).

SELECTION CRITERIA

Randomised controlled trials evaluating the use of preoperative skin antiseptics applied immediately prior to incision in clean surgery. There was no restriction on the inclusion of reports based on language of publication, date or publication status.

DATA COLLECTION AND ANALYSIS

Data extraction and assessment of risk of bias were undertaken independently by two review authors.

MAIN RESULTS

There were no new studies added to the review in the third updateThirteen studies were included in this review (2,623 participants). These evaluated several different types of skin antiseptics - leading to 11 different comparisons being made. Although the antiseptics evaluated differed between studies, all trials involved some form of iodine. Iodine in alcohol was compared to alcohol alone in one trial; one trial compared povidone iodine paint (solution type not reported) with soap and alcohol. Six studies compared different types of iodine-containing products with each other and five compared iodine-containing products with chlorhexidine-containing products.There was evidence from one study suggesting that preoperative skin preparation with 0.5% chlorhexidine in methylated spirits led to a reduced risk of SSI compared with an alcohol based povidone iodine solution: RR 0.47 (95% CI 0.27 to 0.82). However, it is important to note that the trial does not report important details regarding the interventions (such as the concentration of povidone iodine paint used) and trial conduct, such that risk of bias was unclear.There were no other statistically significant differences in SSI rates in the other comparisons of skin antisepsis. Overall the risk of bias in included studies was unclear.A mixed treatment comparison meta-analysis was conducted and this suggested that alcohol-containing products had the highest probability of being effective - however, again the quality of this evidence was low.

AUTHORS' CONCLUSIONS

A comprehensive review of current evidence found some evidence that preoperative skin preparation with 0.5% chlorhexidine in methylated spirits was associated with lower rates of SSIs following clean surgery than alcohol-based povidone iodine paint. However this single study was poorly reported. Practitioners may therefore elect to consider other characteristics such as costs and potential side effects when choosing between alternatives.The design of future trials should be driven by the questions of high priority to decision makers. It may be that investment in at least one large trial (in terms of participants) is warranted in order to add definitive and hopefully conclusive data to the current evidence base. Ideally any future trial would evaluate the iodine-containing and chlorhexidine-containing solutions relevant to current practice as well as the type of solution used (alcohol vs. aqueous).

https://www.ncbi.nlm.nih.gov/pubmed/25897764

Infection Control And Hospital Epidemiology • June 2012

Effects of Preoperative Skin Preparation on Postoperative Wound Infection Rates A Prospective Study of 3 Skin Preparation Protocols

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Abstract

OBJECTIVE—To compare the effects of different skin preparation solutions on surgical-site infection rates.
DESIGN—Three skin preparations were compared by means of a sequential implementation design. Each agent was adopted as the preferred modality for a 6-month period for all general surgery cases. Period 1 used a povidone-iodine scrub-paint combination (Betadine) with an isopropyl alcohol application between these steps, period 2 used 2% chlorhexidine and 70% isopropyl alcohol (ChloraPrep), and period 3 used iodine povacrylex in isopropyl alcohol (DuraPrep). Surgical-site infections were tracked for 30 days as part of ongoing data collection for the National Surgical Quality Improvement Project initiative. The primary outcome was the overall rate of surgical-site infection by 6-month period performed in an intent-to-treat manner.
SETTING—Single large academic medical center. PATIENTS—All adult general surgery patients.
RESULTS—The study comprised 3,209 operations. The lowest infection rate was seen in period 3, with iodine povacrylex in isopropyl alcohol as the preferred preparation method (3.9%, compared with 6.4% for period 1 and 7.1% for period 2; P = .002). In subgroup analysis, no difference in outcomes was seen between patients prepared with povidone-iodine scrub-paint and those prepared with iodine povacrylex in isopropyl alcohol, but patients in both these groups had significantly lower surgical-site infection rates, compared with rates for patients prepared with 2% chlorhexidine and 70% isopropyl alcohol (4.8% vs 8.2%; P = .001).
CONCLUSIONS—Skin preparation solution is an important factor in the prevention of surgical- site infections. Iodophor-based compounds may be superior to chlorhexidine for this purpose in general surgery patients.

Full text, graphs, charts and 21 references

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3371364/pdf/nihms377953.pdf

Journal Of Womens Health • March 2011

Chlorhexidine and alcohol versus povidone-iodine for antisepsis in gynecological surgery

Author information

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Abstract

BACKGROUND

Surgical site infections (SSIs) cause severe morbidity and are associated with tremendous health costs. Skin antisepsis (cleansing) with chlorhexidine and alcohol solutions has demonstrated superiority to povidone-iodine in a variety of surgical interventions. Our objective was to determine if chlorhexidine and alcohol antisepsis protocol reduces the rate of SSIs in elective gynecological laparotomies compared with povidone-iodine antisepsis.

METHODS

This retrospective study was carried out at the Department of Gynecology in a tertiary medical center in Tel Aviv. Patients undergoing elective gynecological laparotomies during two periods of time and who were treated with two different antisepsis protocols were included. The protocols for antisepsis were povidone-iodine 10% scrub followed by 10% povidone-iodine in 65% alcohol (n=145) and chlorhexidine 2% followed by 70% alcohol (n=111). The rate of SSIs as defined by the Centers for Disease Control and Prevention (CDC), and the risk factors for the occurrence of SSIs were calculated.

RESULTS

Antisepsis with chlorhexidine and alcohol was associated with a reduction in the overall rate of SSIs from 14.6% to 4.5% compared with the povidone-iodine protocol (p=0.011). The two groups of patients were similar in regard to baseline characteristics and medical history. Surgical procedures as well as the type of cut, drains, and tension suture use were similar in the two groups. Patients with SSIs tended to be older and heavier. Risk factors found to be associated with SSIs were hypertension, noninsulin-dependent diabetes mellitus (NIDDM), immunodeficiency, and the use of the povidone-iodine antisepsis protocol.

CONCLUSIONS

This retrospective study demonstrates that antisepsis with chlorhexidine and alcohol was associated with a significant reduction in the rate of SSIs compared to povidone-iodine antisepsis in patients undergoing elective gynecological laparotomies. This is of extreme clinical importance, as a change in antisepsis protocol can significantly reduce the morbidity and healthcare costs associated with patients undergoing elective gynecological surgery.

https://www.ncbi.nlm.nih.gov/pubmed/21323582

New England Journal Of Medicine • January 2010

Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis

Author information

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Abstract

BACKGROUND

Since the patient's skin is a major source of pathogens that cause surgical-site infection, optimization of preoperative skin antisepsis may decrease postoperative infections. We hypothesized that preoperative skin cleansing with chlorhexidine-alcohol is more protective against infection than is povidone-iodine.

METHODS

We randomly assigned adults undergoing clean-contaminated surgery in six hospitals to preoperative skin preparation with either chlorhexidine-alcohol scrub or povidone-iodine scrub and paint. The primary outcome was any surgical-site infection within 30 days after surgery. Secondary outcomes included individual types of surgical-site infections.

RESULTS

A total of 849 subjects (409 in the chlorhexidine-alcohol group and 440 in the povidone-iodine group) qualified for the intention-to-treat analysis. The overall rate of surgical-site infection was significantly lower in the chlorhexidine-alcohol group than in the povidone-iodine group (9.5% vs. 16.1%; P=0.004; relative risk, 0.59; 95% confidence interval, 0.41 to 0.85). Chlorhexidine-alcohol was significantly more protective than povidone-iodine against both superficial incisional infections (4.2% vs. 8.6%, P=0.008) and deep incisional infections (1% vs. 3%, P=0.05) but not against organ-space infections (4.4% vs. 4.5%). Similar results were observed in the per-protocol analysis of the 813 patients who remained in the study during the 30-day follow-up period. Adverse events were similar in the two study groups.

CONCLUSIONS

Preoperative cleansing of the patient's skin with chlorhexidine-alcohol is superior to cleansing with povidone-iodine for preventing surgical-site infection after clean-contaminated surgery.

ClinicalTrials.gov number NCT00290290

https://www.ncbi.nlm.nih.gov/pubmed/20054046

British Journal Of Surgery • November 2010

Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery

Author information

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Abstract

BACKGROUND

Surgical-site infection increases morbidity, mortality and financial burden. The preferred topical antiseptic agent (chlorhexidine or povidone-iodine) for preoperative skin cleansing is unclear.

METHODS

A meta-analysis of clinical trials was conducted to determine whether preoperative antisepsis with chlorhexidine or povidone-iodine reduced surgical-site infection in clean-contaminated surgery.

RESULTS

The systematic review identified six eligible studies, containing 5031 patients. Chlorhexidine reduced postoperative surgical-site infection compared with povidone-iodine (pooled odds ratio 0.68, 95 per cent confidence interval 0.50 to 0.94; P = 0.019) .

CONCLUSION

Chlorhexidine should be used preferentially for preoperative antisepsis in clean-contaminated surgery.

https://www.ncbi.nlm.nih.gov/pubmed/20878942

Cochrane Database Of Systematic Reviews • January 2008

Surgical hand antisepsis to reduce surgical site infection

Author information

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Abstract

BACKGROUND

Surgical hand antisepsis, to destroy transient micro-organisms and inhibit the growth of resident micro-organisms, is routinely carried out before undertaking invasive procedures. Antisepsis may reduce the risk of surgical site infections in patients.

OBJECTIVES

To determine the effects of surgical hand antisepsis on the number of surgical site infections (SSIs) in patients. The secondary objective is to determine the effects of surgical hand antisepsis on the numbers of colony forming units (CFUs) of bacteria on the hands of the surgical team.

SEARCH STRATEGY

We searched the Cochrane Wounds Group Specialised Register (June 2007), the Cochrane Central Register of Controlled Trials (Issue 2, 2007), MEDLINE (Week 5, 2007), CINAHL (June 2007), EMBASE (Week 23, 2007) and ZETOC (2005).

SELECTION CRITERIA

Randomised controlled trials comparing surgical hand antisepsis of varying duration, methods and antiseptic solutions.

DATA COLLECTION AND ANALYSIS

Three authors independently assessed studies for selection, trial quality and extracted data.

MAIN RESULTS

Ten trials were included in this review. Only one trial reported the primary outcome, rates of SSIs, and nine trials measured numbers of CFUs. One trial involving 4387 patients found alcohol rubs with additional active ingredients were as effective as aqueous scrubs in reducing SSIs. Four trials compared different alcohol rubs containing additional active ingredients with aqueous scrubs for numbers of CFUs on hands. One trial found N-duopropenide more effective than chlorhexidine and povidone iodine aqueous scrubs. One trial found 45% propanol-2, 30% propanol-1 with 0.2% ethylhexadecyldimethyl ammonium ethylsulfate more effective than chlorhexidine scrubs. One trial found no difference between 1% chlorhexidine gluconate in 61% ethyl alcohol or zinc pyrithione in 70% ethyl alcohol against aqueous povidone iodine. A fourth trial found 4% chlorhexidine gluconate scrubs more effective than chlorhexidine in 70% alcohol rubs. Four trials compared the relative effects of different aqueous scrubs in reducing CFUs on hands. Three trials found chlorhexidine gluconate scrubs were significantly more effective than povidone iodine scrubs. One trial found no difference between chlorhexidine gluconate scrubs and povidone iodine plus triclosan scrubs. Two trials found no evidence of a difference between alternative alcohol rubs in terms of the number of CFUs. Four trials compared the effect of different durations of scrubs and rubs on the numbers of CFUs on hands. One trial found no difference after the initial scrub but found subsequent three minute scrubs using chlorhexidine significantly more effective than subsequent scrubs lasting 30 seconds. One trial found that following a one minute hand wash, a three minute rub appears to be more effective than the five minute rub using alcohol disinfectant. The other comparisons demonstrated no difference.

AUTHORS' CONCLUSIONS

Alcohol rubs used in preparation for surgery by the scrub team are as effective as aqueous scrubbing in preventing SSIs however this evidence comes from only one, equivalence, cluster trial which did not appear to adjust for clustering. Four comparisons suggest that alcohol rubs are at least as, if not more, effective than aqueous scrubs though the quality of these is mixed and each study presents a different comparison, precluding meta analysis. There is no evidence to suggest that any particular alcohol rub is better than another. Evidence from 4 studies suggests that chlorhexidine gluconate based aqueous scrubs are more effective than povidone iodine based aqueous scrubs in terms of the numbers of CFUs on the hands. There is limited evidence regarding the effects on CFUs numbers of different scrub durations. There is no evidence regarding the effect of equipment such as brushes and sponges.

https://www.ncbi.nlm.nih.gov/pubmed/18254046

“This article reviews the studies that have assessed the efficacy of povidone-iodine in hand disinfection and skin preparation and its use as an antiseptic irrigant.”

International Wound Journal • June 2008

Povidone-iodine: use in hand disinfection, skin preparation and antiseptic irrigation

Author information

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Abstract

Iodine and its antibacterial properties have been used for the prevention or management of wound infections for over 150 years. However, the use of solutions (tincture) of iodine has been replaced by the widespread use of povidone-iodine, a water-soluble compound, which is a combination of molecular iodine and polyvinylpyrrolidone. The resultant broad spectrum of antimicrobial activity is well documented and its efficacy, particularly in relation to resistant micro-organisms such as methicillin-resistant Staphylococcus aureus, has been shown. In the clinical environment, there is no general agreement regarding the ‘best’ antiseptic and the practice varies widely. This article reviews the studies that have assessed the efficacy of povidone-iodine in hand disinfection and skin preparation and its use as an antiseptic irrigant. Although there is a distinct lack of well-designed, randomised controlled trials evaluating antiseptic efficacy, selection should be based on the next best available evidence. This evidence suggests that the use of povidone-iodine as an agent of choice is dependent on the clinical need but is also likely to be influenced by personal preference.

http://www.ncbi.nlm.nih.gov/pubmed/18593388

Dermatology • December 2006

Quality control in chronic wound management: the role of local povidone-iodine (Betadine) therapy

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Abstract

BACKGROUND:
The treatment of venous leg ulcers is often inadequate, because of incorrect diagnosis, overuse of systemic antibiotics and inadequate use of compression therapy. Stasis dermatitis related to chronic venous insufficiency accompanied by infected superficial ulcers must be differentiated from erysipelas, cellulitis and contact eczema.

OBJECTIVES
To assess the effectiveness of (1) topical povidone-iodine with and (2) without compression bandages, (3) to compare the efficacy of systemic antibiotics and topical antimicrobial agents to prevent the progression of superficial skin ulcers.

PATIENTS AND METHODS
63 patients presenting ulcerated stasis dermatitis due to deep venous refluxes were included in the study. The clinical stage of all patients was homogeneous determined by clinical, aetiological, anatomical and pathological classification. They were examined by taking a bacteriological swab from their ulcer area. Compression bandages were used in a total of 42 patients. Twenty-one patients with superficial infected (Staphylococcus aureus) ulcers were treated locally with povidone-iodine (Betadine), and 21 patients were treated with systemic antibiotics (amoxicillin). Twenty-one patients were treated locally with Betadine but did not use compression. The end point was the time of ulcus healing. The healing process of the ulcers was related to the impact of bacterial colonization and clinical signs of infection.

RESULTS
Compression increases the ulcer healing rate compared with no compression. Using the same local povidone-iodine (Betadine) treatment with compression bandages is more effective (82%) for ulcus healing than without compression therapy (62%). The healing rate of ulcers treated with systemic antibiotics was not significantly better (85%) than that of the Betadine group. Using systemic antibiotics, the relapse rate of superficial bacterial infections (impetigo, folliculitis) was significantly higher (32%) than in patients with local disinfection (11%).

CONCLUSION
Compression is essential in the mobilization of the interstitial lymphatic fluid from the region of stasis dermatitis. Topical disinfection and appropriate wound dressings are important to prevent wound infection. Systemic antibiotics are necessary only in systemic infections (fever, lymphangitis, lymphadenopathy, erysipelas).

http://www.ncbi.nlm.nih.gov/pubmed/16490980

“The healing rate of ulcers treated with systemic antibiotics was not significantly better (85%) than that of the Betadine group. Using systemic antibiotics, the relapse rate of superficial bacterial infections (impetigo, folliculitis) was significantly higher (32%) than in patients with local disinfection (11%).”

Anales Espanoles de Pediatria • July 2000

Iodine antiseptics are not harmless

Author information

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Abstract

“The use of iodine-containing antiseptics is still common in obstetrics and neonatology. Topical iodine given both to the mother before delivery and to the neonate causes iodine overload. The absorption of maternal iodine through the skin is so fast that iodine in the blood of the umbilical cord increases by 50% a few minutes before delivery. Iodine overload also occurs in the mother. Urinary and breast-milk iodine are increased more than 10-fold in the days after delivery if providone-iodine is used in episiotomy. The overload in the neonate is even higher if breast-fed. Particularly in iodine-deficient areas, this overload can produce thyroid blockade with undesirable effects in congenital hypothyroidism screening, raising the number of false positives and its consequences: parental anxiety and screening costs. The potential effects that this thyroid blockade can produce in the neonate are even more serious. Attention should be drawn to the undesirable effects of iodine antiseptics and their use in the perinatal period should be avoided.”

http://www.ncbi.nlm.nih.gov/pubmed/10998400

“Of the 3,851 blood cultures collected during the study, 120 (3.1%) were contaminated with skin flora. The contamination rate for blood cultures collected after povidone-iodine was 3.8% (74 of 1,947), compared with a rate of 2.4% (46 of 1,904, P = 0.01) after iodine tincture. The difference in mean total hospital costs for patients with contaminated blood cultures and those with sterile blood cultures was $4,100 [per patient] ...”

American Journal Of Medicine • August 1999

A randomized trial of povidone-iodine compared with iodine tincture for venipuncture site disinfection: effects on rates of blood culture contamination

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Abstract

BACKGROUND:
Contamination of blood cultures creates problems in their interpretation and unneeded resource utilization. Because skin flora comprise the major group of contaminant species, more effective skin disinfection at the venipuncture site could reduce contamination.

SUBJECTS AND METHODS
We performed a randomized trial in adult inpatients at a tertiary care teaching hospital. Antecubital venipuncture sites were randomly disinfected with povidone-iodine or iodine tincture, and blood cultures (two bottles, 10 mL of blood) were drawn by professional phlebotomists. Scoring of contaminant species was restricted to skin flora. Hospital resource utilization was compared among patients with contaminated blood cultures and those with sterile blood cultures.

RESULTS
Of the 3,851 blood cultures collected during the study, 120 (3.1%) were contaminated with skin flora. The contamination rate for blood cultures collected after povidone-iodine was 3.8% (74 of 1,947), compared with a rate of 2.4% (46 of 1,904, P = 0.01) after iodine tincture. The difference in mean total hospital costs for patients with contaminated blood cultures and those with sterile blood cultures was $4,100 (95% confidence interval: $740 to $7,400, P = 0.02).

CONCLUSIONS
Iodine tincture is superior to povidone-iodine for venipuncture site antisepsis before blood culture sampling. Because of the high costs associated with contaminated blood cultures, hospitals should consider switching from povidone-iodine to iodine tincture. Reduction of the contamination rate may improve the quality of patient care and reduce hospital costs.

http://www.ncbi.nlm.nih.gov/pubmed/10460041

“On these grounds, a number of clinical fields exist in prophylaxis and therapy, for either once only or repeated applications: the disinfection of hands and skin, mucosa antisepsis, intra- and postoperative wound treatment, therapy of skin infections, burns and chronic wounds.”

Dermatology • December 1997

Povidone-iodine in antisepsis—state of the art

Author information
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Abstract

The natural element iodine has been used for more than 150 years to prevent infection and treat wounds. Yet only due to the development of iodophors has it become possible to use this highly efficient microbicide in a wide range of medical applications. The antimicrobial spectrum is universal. Its efficiency against clinically and epidemiologically significant new pathogens, such as methicillin-resistant Staphylococcus aureus and Enterococcus sp. has also been validated. No development of resistance has been determined. New data are also available on the excellent local tolerability of Betaisodona (povidone-iodine) preparations. On these grounds, a number of clinical fields exist in prophylaxis and therapy, for either once only or repeated applications: the disinfection of hands and skin, mucosa antisepsis, intra- and postoperative wound treatment, therapy of skin infections, burns and chronic wounds.

http://www.ncbi.nlm.nih.gov/pubmed/9403248

“Povidone was responsible for a severe anaphylactic reaction in our patient. The possibility of an iatrogenic adverse effect caused by the excipient but not by the active ingredient should be considered in patients exhibiting similar symptoms. We believe that the excipients used in the preparation of all medicines should be disclosed.”

Annals In Pharmacotherapy • January 1996

Anaphylactic shock following povidone

Author information
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Abstract

OBJECTIVE
To report a patient with an anaphylactic reaction related to povidone administration.
CASE SUMMARY
A 37-year-old man with a history of allergic rhinitis presented with urticaria, dyspnea, wheezing, rhinorrhea, and dysphonia 20 minutes after the intraarticular administration of mepivacaine hydrochloride and paramethasone acetate in his right knee. Two months after this episode, he was admitted for controlled provocation tests. Tests on mepivacaine were negative. The preparation of paramethasone contained the excipients benzalkonium chloride, polysorbate 80, and povidone. In vitro tests and provocation were negative with polysorbate 80 and benzalkonium chloride, but positive with povidone.
DISCUSSION
Povidone, a mixture of synthetic polymers, is commonly used as an excipient in pharmaceutical products, an additive in food products, and a dispersant and stabilizer in hairsprays. Although it is well tolerated when used topically or parenterally, local and systemic effects have been reported. Furthermore, multiorgan involvement resulting from accumulation of the drug in the reticuloendothelial system has been described. The immunologic properties of povidone have not been explored in humans, but have been in animals. In fact, the capacity of povidone to release histamine and its immunogenicity are proportional to its molecular weight. An immunoglobulin (Ig) E-mediated hypersensitivity reaction in asthma has been reported. In our case, povidone was responsible for the syndrome. However, we cannot determine the exact mechanism. An unspecific histamine release and/or an IgE-mediated hypersensitivity could be involved.
CONCLUSIONS
Povidone was responsible for a severe anaphylactic reaction in our patient. The possibility of an iatrogenic adverse effect caused by the excipient but not by the active ingredient should be considered in patients exhibiting similar symptoms. We believe that the excipients used in the preparation of all medicines should be disclosed.

http://www.ncbi.nlm.nih.gov/pubmed/8773164

CHAPTER FOURTEEN

Coconut Oil

The Peer Review

Proven Health Facts Related To Coconut Oil

The unique combination of fatty acids in organic, cold pressed coconut oil can have profound positive effects on health. This includes fat loss, better brain function and various other amazing benefits. Listed below, before we get into the peer review, are some of the health benefits of coconut oil that have been experimentally confirmed in human studies.

Coconut Oil Contains a Unique Combination of Fatty Acids With Powerful Medicinal Properties

Coconut oil has been demonized in the past because it contains saturated fat. In fact, coconut oil is one of the richest sources of saturated fat known to man, with almost 90% of the fatty acids in it being saturated. However, new data is showing that saturated fats are harmless. Many massive studies that include hundreds of thousands of people prove that the whole "artery-clogging" idea was false. Additionally, coconut oil doesn't contain your average run-of-the-mill saturated fats like you would find in cheese or steak. Coconuts contain so-called Medium Chain Triglycerides (MCTs) – which are fatty acids of a medium length. Most of the fatty acids in the diet are long-chain fatty acids, but the medium-chain fatty acids in coconut oil are metabolized differently. They go straight to the liver from the digestive tract, where they are used as a quick source of energy or turned into so-called ketone bodies, which can have therapeutic effects on brain disorders like epilepsy and Alzheimer's.

Populations That Eat a lot of Coconut Are Among The Healthiest People on The Planet

Coconut is kind of an "exotic" food in the Western world, primarily consumed by health conscious people. However, in some parts of the world, coconut is a dietary staple that people have thrived on for many generations. The best example of such a population is the Tokelauans, which live in the South Pacific. They eat over 60% of their calories from coconuts and are the biggest consumers of saturated fat in the world. These people are in excellent health, with no evidence of heart disease. Another example of a population that eats a lot of coconut and remains in excellent health is the Kitavans.

Coconut Oil Can Increase Your Energy Expenditure, Helping You Burn More Fat

Obesity is currently one of the biggest health problems in the world. While some people think obesity is only a matter of calories, others believe that the sources of

those calories are critical too. It is a fact that different foods affect our bodies and hormones in different ways. In this regard, a calorie is NOT a calorie. The medium-chain triglycerides (MCTs) in coconut oil can increase energy expenditure compared to the same amount of calories from longer chain fats. One study found that 15-30 grams of MCTs per day increased 24 hour energy expenditure by 5%, totalling about 120 calories per day.

The Lauric Acid in Coconut Oil Can Kill Bacteria, Viruses and Fungi, Helping to Stave Off Infections

Almost 50% of the fatty acids in coconut oil is the 12-carbon Lauric Acid. When coconut oil is enzymatically digested in the gut, it also forms a monoglyceride called monolaurin. Both lauric acid and monolaurin can kill harmful pathogens like bacteria, viruses and fungi. For example, these substances have been shown to kill the bacteria Staphylococcus Aureus (a very dangerous pathogen) and the yeast Candida Albicans, a common source of yeast infections in humans.

Coconut Oil Can Kill Your Hunger Making You Eat Less Without Even Trying

One interesting feature of coconut oil is that it can reduce your hunger. This may be related to the way the fatty acids in it are metabolized, because ketone bodies can have an appetite reducing effect. In one study, varying amounts of medium and long chain triglycerides were fed to 6 healthy men. The men eating the most MCTs ate 256 fewer calories per day, on average. Another study in 14 healthy men discovered that those who ate the most Medium Chain Triglycerides at breakfast ate significantly fewer calories at lunch. These studies were small and only done for a short period of time. If this effect were to persist over the long term, it could have a dramatic influence on body weight over a period of several years.

The Fatty Acids in Coconut Oil Are Turned into Ketones, Which Can Reduce Seizures

A so-called ketogenic (very low carb, very high fat) diet is currently being studied to treat various disorders. The best known therapeutic application of this diet is treating drug-resistant epilepsy in children. This diet involves eating very little carbohydrates and large amounts of fat, leading to greatly increased concentrations of ketone bodies in the blood. For some reason, this diet can dramatically reduce the rate of seizures in epileptic children, even those who haven't had success with multiple different types of drugs. Because the MCTs in coconut oil get shipped to the liver and turned into ketone bodies, they are often used in epileptic patients to induce ketosis while allowing for a bit more carbs in the diet. It should also be noted that from an evolutionary perspective the human species once obtained all energy from fats. Over the last 100 years sugar has been added to everything. Everything from bread to pickles, from mayonnaise to salad dressing to juices, including soda which accounts for a massive sugar intake. The human evolutionary process has been mutated—to obtaining energy from sugar rather than fat and the consequences aren't just sluggishness or lack of energy but numerous diseases and disorders.

Coconut Oil Can Improve Blood Cholesterol Levels and May Lower Your Risk of Heart Disease

Coconut oil is loaded with saturated fats, which actually do not harm the blood lipid profile like previously thought. Saturated fats raise HDL, the good cholesterol, and change the LDL cholesterol, the bad cholesterol, to a benign subtype. In one study in 40 women, coconut oil reduced Total and LDL cholesterol while increasing HDL compared to soybean oil. There are also rat studies showing that coconut oil reduces triglycerides, total and LDL cholesterol, increases HDL and improves blood coagulation factors and antioxidant status. These are all important factors related to long-term health. This improvement in cardiovascular risk factors should theoretically lead to a reduced risk of heart disease over the long term.

Coconut Oil Can Protect Hair Against Damage, Moisturize Skin and Function as Sunscreen

Coconut oil can serve various purposes that have nothing to do with eating it. Many people are using it for cosmetic purposes and to improve the health and appearance of their skin and hair. Studies on individuals with dry skin show that coconut oil can improve the moisture and lipid content of the skin. Coconut oil can also be very protective against hair damage and one study shows effectiveness as sunscreen, blocking about 20% of the sun's ultraviolet rays. Another application is using it like mouthwash in a process called oil pulling, which can kill some of the harmful bacteria in the mouth, improve dental health and reduce bad breath.

The Fatty Acids in Coconut Oil Can Boost Brain Function in Alzheimer's Patients

Alzheimer's disease is the most common cause of dementia worldwide and occurs primarily in elderly individuals. In Alzheimer's patients, there appears to be a reduced ability to use glucose for energy in certain parts of the brain. Ketone bodies can supply energy for the brain and researchers have speculated that ketones can provide an alternative energy source for these malfunctioning cells and reduce the symptoms of Alzheimer's. In one 2006 study, consumption of medium chain triglycerides led to immediate improvement in brain function in patients with milder forms of Alzheimer's. Other studies support these findings and medium chain triglycerides are being intensively studied as potential therapeutic agents in Alzheimer's disease.

Coconut Oil Can Help You Lose Fat, Especially The Dangerous Fat in Your Abdominal Cavity

Given that coconut oil can reduce appetite and increase fat burning, it makes sense that it can also help you lose weight. Coconut oil appears to be especially effective in reducing abdominal fat, which lodges in the abdominal cavity and around organs. This is the most dangerous fat of all and is highly associated with many Western diseases. Waist circumference is easily measured and is a great marker for the amount of fat in the abdominal cavity. A study in 40 women with abdominal obesity, supplementing with 30 mL (1 ounce) of coconut oil per day lead to a significant reduction in both BMI and waist circumference in a period of just 12 weeks. Another study in 20 obese males noted a reduction in waist circumference of 2.86 cm (1.1 inches) after 4 weeks of 30 mL (1 ounce) of coconut oil per day. This number may not seem too impressive on the surface, but be aware that these people aren't adding exercise or restricting calories. They're losing significant amounts of abdominal fat simply by adding coconut oil to their diet.

Asian Pacific Journal Of Tropical Medicine • March 2011

Coconut (Cocos nucifera L.: Arecaceae): in health promotion and disease prevention

Author information

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Abstract

Coconut, Cocos nucifera L., is a tree that is cultivated for its multiple utilities, mainly for its nutritional and medicinal values. The various products of coconut include tender coconut water, copra, coconut oil, raw kernel, coconut cake, coconut toddy, coconut shell and wood based products, coconut leaves, coir pith etc. Its all parts are used in someway or another in the daily life of the people in the traditional coconut growing areas. It is the unique source of various natural products for the development of medicines against various diseases and also for the development of industrial products. The parts of its fruit like coconut kernel and tender coconut water have numerous medicinal properties such as antibacterial, antifungal, antiviral, antiparasitic, antidermatophytic, antioxidant, hypoglycemic, hepatoprotective, immunostimulant. Coconut water and coconut kernel contain microminerals and nutrients, which are essential to human health, and hence coconut is used as food by the peoples in the globe, mainly in the tropical countries. The coconut palm is, therefore, eulogised as 'Kalpavriksha' (the all giving tree) in Indian classics, and thus the current review describes the facts and phenomena related to its use in health and disease prevention.

Full text, PDF, graphs, charts and 49 references

Scroll down for a link to the PDF

http://www.sciencedirect.com/science/article/pii/S1995764511600783

The following benefits of coconut oil are described

As an electrolyte	Antiviral effect
Antidote effect	Antifungal effect
Antioxidant effect	Antiprotozoal activity
Cardioprotective effect	Anticancer effect
Antithrombotic effect	Immunostimulatory effect
Antiatherosclerotic effect	Antidiabetic effect
Hypolipidemic effect	Hepatoprotective activity
Anticholecystitic effect	Disinfectant activity
Antibacterial activity	Insect repellant
Anticaries activity	Eco-friendly biodiesel
Antidermatophytic activity	Hormone like effect

British Journal Of Nutrition • July 2015

The role of dietary coconut for the prevention and treatment of Alzheimer's disease: potential mechanisms of action

Author information

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Abstract

"Coconut, Cocos nucifera L., is a tree that is cultivated to provide a large number of products, although it is mainly grown for its nutritional and medicinal values. Coconut oil, derived from the coconut fruit, has been recognised historically as containing high levels of saturated fat; however, closer scrutiny suggests that coconut should be regarded more favourably. Unlike most other dietary fats that are high in long-chain fatty acids, coconut oil comprises medium-chain fatty acids (MCFA). MCFA are unique in that they are easily absorbed and metabolised by the liver, and can be converted to ketones. Ketone bodies are an important alternative energy source in the brain, **and may be beneficial to people developing or already with memory impairment, as in Alzheimer's disease (AD)**. Coconut is classified as a highly nutritious 'functional food'. It is rich in dietary fibre, vitamins and minerals; however, notably, evidence is mounting to support the concept that coconut may be beneficial in the treatment of obesity, dyslipidaemia, elevated LDL, insulin resistance and hypertension - these are the risk factors for CVD and type 2 diabetes, and also for AD. In addition, phenolic compounds and hormones (cytokinins) found in coconut may assist in preventing the aggregation of amyloid-ß peptide, potentially inhibiting a key step in the pathogenesis of AD. The purpose of the present review was to explore the literature related to coconut, outlining the known mechanistic physiology, and to discuss the potential role of coconut supplementation as a therapeutic option in the prevention and management of AD."

http://www.ncbi.nlm.nih.gov/pubmed/25997382

“This study, although preliminary, demonstrated the positive influence of coconut oil at the cognitive level of patients with Alzheimer’s, this improvement being dependent on sex, presence or absence of diabetes and degree of dementia.”

Nutricion Hospitalaria • December 2015

Coconut Oil: Non-Alternative Drug Treatment Against Alzheimer’s Disease

Author information

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2. Universidad Europea de Valencia
3. Hospital Universitario Morales Meseguer
4. Universidad de Valencia. España

Abstract

BACKGROUND

Alzheimer’s dementia is the most prevalent nowadays. As for treatment, there is no definitive cure drug, thus new therapies are needed. In this regard the medium chain triglycerides are a direct source of cellular energy and can be a nonpharmacological alternative to the neuronal death for lack of it, that occurs in Alzheimer patients.

OBJECTIVE

To evaluate the impact of coconut oil in the development of Alzheimer’s dementia, in any degree of dementia. Also determine whether this improvement influences within variables such as sex and suffering or not Type II Diabetes Mellitus.

MATERIAL AND METHODS

A prospective study was conducted in patients with Alzheimer’s dementia, with a control and an intervention group which was administered 40 ml/day of extra virgin coconut oil. The parameters evaluated were the mini test scores Lobo cognitive test, pre and post intervention in both groups.

RESULTS

It was observed in subjects taking the product, a statistically significant increase in test score MECWOLF and therefore an improvement in cognitive status, improving especially women’s, those without diabetes mellitus type II, and severe patients.

CONCLUSION

This study, although preliminary, demonstrated the positive influence of coconut oil at the cognitive level of patients with Alzheimer’s, this improvement being dependent on sex, presence or absence of diabetes and degree of dementia.

Full text, PDF, graphs, charts and 25 references

http://www.aulamedica.es/nh/pdf/9707.pdf

“These results suggest the potential value of Virgin coconut oil as an antistress functional oil.”

Experimental And Therapeutic Medicine • January 2015

Antistress and antioxidant effects of virgin coconut oil in vivo

Author information

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Abstract

Virgin coconut oil (VCO) has been consumed worldwide for various health-related reasons and some of its benefits have been scientifically evaluated. Medium-chain fatty acids were found to be a potential antidepressant functional food; however, this effect had not been evaluated in VCO, which is rich in polyphenols and medium-chain fatty acids. The aim of this study was to evaluate the antistress and antioxidant effects of VCO in vivo, using mice with stress-induced injury. The antistress effect of VCO (administered per os, at a dose of 10 ml/kg body weight) was evaluated using the forced swim test and chronic cold restraint stress models. VCO was able to reduce immobility time and restore oxidative stress in mice post-swim test. Furthermore, mice treated with VCO were found to exhibit higher levels of brain antioxidants, lower levels of brain 5-hydroxytryptamine and reduced weight of the adrenal glands. Consequently, the serum cholesterol, triglyceride, glucose and corticosterone levels were also lower in VCO-treated mice. These results suggest the potential value of VCO as an antistress functional oil.

Full text with 12 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4247320/

Postgrad Medicine • November 2014

Virgin coconut oil and its potential cardioprotective effects

Author information

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Abstract

“Emphasis on diet to improve the cardiovascular (CV) risk profile has been the focus of many studies. Recently, virgin coconut oil (VCO) has been growing in popularity due to its potential CV benefits. The chemical properties and the manufacturing process of VCO make this oil healthier than its copra-derived counterpart. This review highlights the mechanism through which saturated fatty acids contribute to CV disease (CVD), how oils and fats contribute to the risk of CVD, and the existing views on VCO and how its cardioprotective effects may make this a possible dietary intervention in isolation or in combination with exercise to help reduce the burden of CVDs.”

http://www.ncbi.nlm.nih.gov/pubmed/25387216

“In conclusion, Virgin Coconut Oil prevented lipid peroxidation and increased the antioxidant enzymes in the osteoporotic rat model.”

Evidence Based Complementary Alternative Medicine • August 2012

The effects of virgin coconut oil on bone oxidative status in ovariectomised rat

Abujazia MA1, Muhammad N, Shuid AN, Soelaiman IN.

Abstract

Virgin coconut oil (VCO) was found to have antioxidant property due to its high polyphenol content. The aim of this study was to investigate the effect of the virgin coconut oil on lipid peroxidation in the bone of an osteoporotic rat model. Normal female Sprague-Dawley rats aged 3 months old were randomly divided into 4 groups, with 8 rats in each group: baseline, sham, ovariectomised (OVX) control group, and OVX given 8% VCO in the diet for six weeks. The oxidative status of the bone was assessed by measuring the index of lipid peroxidation, which is malondialdehyde (MDA) concentration, as well as the endogenous antioxidant enzymes glutathione peroxidase (GPX) and superoxide dismutase (SOD) in the tibia at the end of the study. The results showed that there was a significant decrease in MDA levels in the OVX-VCO group compared to control group. Ovariectomised rats treated with VCO also had significantly higher GPX concentration. The SOD level seemed to be increased in the OVX-VCO group compared to OVX-control group. In conclusion, VCO prevented lipid peroxidation and increased the antioxidant enzymes in the osteoporotic rat model.

http://www.ncbi.nlm.nih.gov/pubmed/22927879

“To summarize our findings, virgin coconut oil effectively improved bone structure and prevented bone loss in osteoporosis animal model. The beneficial effects of virgin coconut oil on bone microarchitecture may be due to the high polyphenols which exert antioxidant property. Virgin coconut oil could offer an interesting approach to prevent accelerated bone loss in osteoporosis especially in postmenopausal women.”

Evidence Based Complementary Alternative Medicine • September 2012

Virgin coconut oil supplementation prevents bone loss in osteoporosis rat model

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Abstract

Oxidative stress and free radicals have been implicated in the pathogenesis of osteoporosis. Therefore, antioxidant compounds have the potential to be used in the prevention and treatment of the disease. In this study, we investigated the effects of virgin coconut oil (VCO) on bone microarchitecture in a postmenopausal osteoporosis rat model. VCO is a different form of coconut oil as it is rich with antioxidants. Three-month-old female rats were randomly grouped into baseline, sham-operated, ovariectomized control (Ovx), and ovariectomized rats fed with 8% VCO in their diet for six weeks (Ovx+VCO). Bone histomorphometry of the right femora was carried out at the end of the study. Rats supplemented with VCO had a significantly greater bone volume and trabecular number while trabecular separation was lower than the Ovx group. In conclusion, VCO was effective in maintaining bone structure and preventing bone loss in estrogen-deficient rat model.

“To summarize our findings, virgin coconut oil effectively improved bone structure and prevented bone loss in osteoporosis animal model. The beneficial effects of VCO on bone microarchitecture may be due to the high polyphenols which exert antioxidant property. Virgin coconut oil could offer an interesting approach to prevent accelerated bone loss in osteoporosis especially in postmenopausal women.”

Full Text with 62 References:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3457741/

“These results suggested that Virgin Coconut Oil supplementation possesses a cardioprotective effect by preventing the increase in blood pressure via an antioxidant mechanism ...”

Pharmaceutical Biology • April 2015

Cardioprotective effect of virgin coconut oil in heated palm oil diet-induced hypertensive rats

Author information

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Abstract

CONTEXT

Virgin coconut oil (VCO) contains high antioxidant activity which may have protective effects on the heart in hypertensive rats.

OBJECTIVES

The study investigated the effects of VCO on blood pressure and cardiac tissue by measuring angiotensin-converting enzyme (ACE) activity and its histomorphometry in rats fed with a heated palm oil (HPO) diet.

MATERIALS AND METHODS

Thirty-two male Sprague-Dawley rats were randomly divided into four groups: (i) control, (ii) orally given VCO (1.42 ml/kg), (iii) fed with a HPO (15%) diet, and (iv) fed with a HPO diet and supplemented with VCO (1.42 ml/kg, po) (HPO+VCO) for 16 weeks. Blood pressure was measured monthly. After 16 weeks, rat hearts were dissected for lipid peroxidation (TBARS) and ACE activity measurement and histomorphometric study.

RESULTS

Systolic blood pressure was significantly increased in the HPO group compared with the control starting at week eight (112.91 ± 1.32 versus 98.08 ± 3.61 mmHg, $p < 0.05$) which was prevented by VCO supplementation (91.73 ± 3.42 mmHg). The consumption of HPO increased TBARS and ACE activity in heart, which were inhibited by VCO supplementation. The increases in the myofiber width and area as well as nuclear size reduction in the HPO group were significantly prevented by VCO supplementation.

CONCLUSION

These results suggested that VCO supplementation possesses a cardioprotective effect by preventing the increase in blood pressure via an antioxidant mechanism and remodeling in rats fed repeatedly with a HPO diet.

http://www.ncbi.nlm.nih.gov/pubmed/25853965

“The aim of this study is to quantify the cytokinin compounds from different maturation stages of coconut water. Two local coconut varieties were chosen, namely Malayan Green Dwarf (MGD) and Malayan Yellow Dwarf (MYD).”

Quantification of Cytokinins in Coconut Water from Different Maturation Stages of Malaysia’s Coconut (Cocos nucifera L.) Varieties

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Introduction

Coconut water (coconut liquid endosperm) is widely consumed around the world since it is refreshing, high in nutritional values and contains many potential therapeutic properties [1]. It was believed that coconut water is useful in the treatment of many health problems, including dehydration, digestive problems, fatigue, diarrhoea, kidney stones and constipation [2]. It also uses as a growth promoting supplement in plant tissue culture industry [3]. Phytohormones, particularly cytokinins, one of the most interesting components reported present in coconut water. Previous findings had shown some significant anti-aging, anti-carcinogenic and anti-thrombotic effects that contributed to the various health benefits [4]. N6-isopentenyladenine, dihydrozeatin, trans-zeatin, kinetin, ortho-topolin, dihydrozeatin O-glucoside, trans-zeatin O-glucoside, trans-zeatin riboside, kinetin riboside and trans-zeatin riboside-5’-monophosphate are among the cytokinin compounds identified in coconut water [5-7].

The activity of cytokinins is essentially dependent on their chemical structures. All native cytokinins are derivatives of adenine with at least one substituent at the N6 position as summarized in Table 1. The most active cytokinin present in coconut water is trans-zeatin [8]. Recent study has reported that trans-zeatin prevents the formation of amyloid ß-protein, helpful in the treatment of neural diseases [9] and possesses an inhibitory effect on acetylcholinesterase. It can be used to treat Alzheimer’s disease or related neural dysfunctions [10,11]. The most abundant cytokinin present in coconut water is trans-zeatin riboside [12] and this compound was reported capable to impair the viability of neoplastic and colon carcinoma cell lines [13]. DL-dihydrozeatin, another type of cytokinin compounds was reported involved in the regulation of cell division during cereal grain development. It also plays a role as an intermediate in the zeatin biosynthesis [14]. Zeatin was known to have anti-ageing property or serves as youth-preserving agent. This type of cytokinin has no carcinogenic effect because it does not induce cell proliferation. Kinetin (N6-furfuryladenine) [15] was first identified in 1955 and exerts anti-ageing effects in plants, human skin cells and fruitflies [16,17].

Numerous techniques had been utilized to quantify the cytokinins, including gas or liquid chromatography coupled with mass spectrometry (e.g. GC-MS, LC-MS), capillary chromatography such as capillary electrophoresis (CE) and micellar electrokinetic capillary chromatography (MECC) as well as enzyme-linked immunosorbent assays (ELISA) or radioimmunoassays (RIA) [18,19]. Recent advances in instrumentation like ultra-performance liquid chromatography (UPLC) and the range of detectors available nowadays enable analytical scientists to identify and quantify several cytokinins [20-22]. It was known that cytokinins presents in coconut water at a very low concentration, therefore, pre-concentration of the cytokinins was achieved using solid-phase extraction (SPE) with Strata C18-E cartridges [23]. In our study, we have developed an UPLC-PDA method to quantify few cytokinin compounds (trans-zeatin, trans-zeatin riboside, trans-zeatin glucoside, DL-dihydrozeatin and kinetin) in a single run. This analytical approach is more sensitive and able to provide higher efficiency with better separation within a short period of time. The aim of this study is to quantify the cytokinin compounds from different maturation stages of coconut water. Two local coconut varieties were chosen, namely Malayan Green Dwarf (MGD) and Malayan Yellow Dwarf (MYD).

Full text, graphs, charts, photos and 33 references

http://www.omicsonline.org/open-access/quantification-of-cytokinins-in-coconut-water-from-different-maturation-stages-of-malaysias-coconut-cocos-nucifera-l-varieties-2157-7110-1000515.pdf

“Virgin Coconut Oil prevents blood pressure elevation and improves endothelial functions in rats ...”

Evidence Based Complementary Alternative Medicine • June 2013

Virgin coconut oil prevents blood pressure elevation and improves endothelial functions in rats fed with repeatedly heated palm oil

Author information
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Abstract

This study was performed to explore the effects of virgin coconut oil (VCO) in male rats that were fed with repeatedly heated palm oil on blood pressure, plasma nitric oxide level, and vascular reactivity. Thirty-two male Sprague-Dawley rats were divided into four groups: (i) control (basal diet), (ii) VCO (1.42 mL/kg, oral), (iii) five-times-heated palm oil (15%) (5HPO), and (iv) five-times-heated palm oil (15%) and VCO (1.42 mL/kg, oral) (5HPO + VCO). Blood pressure was significantly increased in the group that was given the 5HPO diet compared to the control group. Blood pressure in the 5HPO + VCO group was significantly lower than the 5HPO group. Plasma nitric oxide (NO) level in the 5HPO group was significantly lower compared to the control group, whereas in the 5HPO + VCO group, the plasma NO level was significantly higher compared to the 5HPO group. Aortic rings from the 5HPO group exhibited attenuated relaxation in response to acetylcholine and sodium nitroprusside as well as increased vasoconstriction to phenylephrine compared to the control group. Aortic rings from the 5HPO + VCO group showed only attenuated vasoconstriction to phenylephrine compared to the 5HPO group. In conclusion, VCO prevents blood pressure elevation and improves endothelial functions in rats fed with repeatedly heated palm oil.

Full Text with 35 References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3687594/

“The results demonstrated that blended and interesterified oils of coconut with ground nut oil or olive oil enhance hepatic antioxidant enzymes, decreased lipid peroxidation in liver and reduced the susceptibility of LDL to oxidation.”

Food Chemistry • June 2008

Rats fed blended oils containing coconut oil with groundnut oil or olive oil showed an enhanced activity of hepatic antioxidant enzymes and a reduction in LDL oxidation

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Abstract

The effects of feeding Wistar rats with blended and interesterified oils of coconut (CO):groundnut (GNO) or CO:olive (OLO) on liver antioxidant enzyme activities and susceptibility of LDL to oxidation were studied. The hepatic lipid peroxidation (LPO) levels in the rats fed CO:GNO blend and interesterified oils were increased by 31% and 21%, when compared to the rats given CO. The superoxide dismutase activity was increased by 31% and 28%, and catalase (CAT) activity was increased by 37% and 39%, respectively, in rats given blends and interesterified oils of CO:GNO, as compared to those given CO. The activities of glutathione peroxidase (GPx) were increased by 17% and 20% in rats given CO:GNO blend and interesterified oils. Glutathione transferase (GST) level was also found to be increased by 26% and 31% after feeding blended and interesterified oils of CO:GNO, compared to those given CO. The LDL oxidation, which was elevated by feeding GNO, was found to be reduced by 10% and 14%, respectively, in the groups fed blended and interesterified oils of CO:GNO. Similarly, CO:OLO blended oils enhanced SOD, CAT, GPx and GST activities by 34%, 43%, 27% and 23%, respectively, compared to the rats given CO-containing diets. The corresponding increases in theses antioxidant enzyme activities when CO:OLO interesterified oils were fed to rats were 38%, 50%, 28% and 26%, respectively, when compared to rats given CO-containing diets. There was a significant reduction in hepatic LPO as well as oxidation of LDL, when blended and interesterified oils of CO:OLO were fed to rats. The results demonstrated that blended and interesterified oils of CO with GNO or OLO enhance hepatic antioxidant enzymes, decreased lipid peroxidation in liver and reduced the susceptibility of LDL to oxidation.

http://www.ncbi.nlm.nih.gov/pubmed/26065757

“frequent nut consumption has been associated with lower concentrations of some peripheral inflammation markers in cross-sectional studies.”

Asia Pacific Journal Of Clinical Nutrition • 2008

The effect of nuts on inflammation

Author information

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Abstract

Inflammation is one of the recognised mechanisms involved in the development of atherosclerotic plaque and insulin resistance. Inflammatory or endothelial markers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6), fibrinogen, Vascular Cell Adhesion Molecule-1 (VCAM-1) and Intracellular Adhesion Molecule-1 (ICAM-1) have been identified as independent predictors of cardiovascular disease (CVD) or diabetes in human prospective studies. Epidemiological and clinical studies suggest that some dietary factors, such as n-3 polyunsaturated fatty acids, antioxidant vitamins, dietary fiber, L-arginine and magnesium may play an important role in modulating inflammation. The relationship observed between frequent nut consumption and the reduced risk of cardiovascular mortality and type 2 diabetes in some prospective studies could be explained by the fact that nuts are rich in all of these modulator nutrients. In fact, frequent nut consumption has been associated with lower concentrations of some peripheral inflammation markers in cross-sectional studies. Nut consumption has also been shown to decrease the plasma concentration of CRP, IL-6 and some endothelial markers in recent clinical trials.

Full report, PDF, with 37 references

http://apjcn.nhri.org.tw/server/APJCN/17%20Suppl%201//333.pdf

CHAPTER FIFTEEN

Olive Oil

The Peer Review

Olive oil is a fat obtained from the olive, a traditional tree crop of the Mediterranean Basin. The oil is produced by pressing whole olives and is commonly used in cooking, cosmetics, pharmaceuticals, and soaps, and as a fuel for traditional oil lamps. Olive oil is used throughout the world and is often associated with Mediterranean cuisine and diet.

The olive tree is native to the Mediterranean basin; wild olives were collected by Neolithic peoples as early as the 8th millennium BC. The wild olive tree originated in Asia Minor or in ancient Greece. It is not clear when and where olive trees were first domesticated: in Asia Minor, along the Levantine coast stretching from the Sinai Peninsula and Israel to historic Armenia, or somewhere in the Mesopotamian Fertile Crescent.

Archeological evidence shows that olives were turned into olive oil by 6000 BC and 4500 BC in present-day Israel. Until 1500 BC, eastern coastal areas of the Mediterranean were most heavily cultivated. Evidence also suggests that olives were being grown in Crete as long ago as 2,500 BC. The earliest surviving olive oil amphorae date to 3500 BC (Early Minoan times), though the production of olive oil is assumed to have started before 4000 BC. The cultivation of olive trees in Crete became particularly intense in the post-palatial period and played an important role in the island's economy, as it did across the Mediterranean. Recent genetic studies suggest that species used by modern cultivators descend from multiple wild populations, but a detailed history of domestication is not yet forthcoming.

In 2013, world production of virgin olive oil was 2.8 million tons, a 20% decrease from the 2012 world production of 3.5 million tons. Spain produced 1.1 million tons or 39% of world production in 2013. 75% of Spain's production derives from the region of Andalucía, particularly within Jaén province which produces 70% of olive oil in Spain.

Although Italy is a net importer of olive oil, it produced 442,000 tons in 2013 or 16% of the world's production. Major Italian producers are known as "Città dell'Olio", "oil cities"; including Lucca, Florence and Siena, in Tuscany. The largest production, however, is harvested in Apulia and Calabria. Greece accounted for 11% of world production in 2013. Australia now produces a substantial amount of olive oil. Many Australian producers only make premium oils, while a number of corporate growers operate groves of a million trees or more and produce oils for the general market. Australian olive oil is exported to Asia, Europe and the United States.

In North America, Italian and Spanish olive oils are the best-known, and top-quality extra-virgin olive oil from Italy, Spain, Portugal and Greece are sold at high prices, often in prestige packaging. A large part of U.S. olive oil imports come from Italy, Spain, and Turkey. The United States produces olive oil in California, Arizona, Texas, and Georgia.

Different names for olive oil indicate the degree of processing the oil has undergone as well as the quality of the oil. Extra-virgin olive oil is the highest grade available, followed by virgin olive oil. The word "virgin" indicates that the olives have been pressed to extract the oil; no heat or chemicals have been used during the extraction process, and the oil is pure and unrefined. Virgin olive oils contain the highest levels of polyphenols, antioxidants that have been linked with better health.

Olive Oil, which is sometimes denoted as being "Made from refined and virgin olive oils" is a blend of refined olive oil with a virgin grade of olive oil. Pure, Classic, Light and Extra-Light are terms introduced by manufacturers in countries that are non-traditional consumers of olive oil for these products to indicate both their composition of being only 100% olive oil, and also the varying strength of taste to consumers. Contrary to a common consumer belief, they do not have fewer calories than Extra-virgin oil as implied by the names. Cold pressed or Cold extraction means "that the oil was not heated over a certain temperature (usually 27 °C (80 °F)) during processing, thus retaining more nutrients and undergoing less degradation". The difference be-

tween Cold Extraction and Cold Pressed is regulated in Europe, where the use of a centrifuge, the modern method of extraction for large quantities, must be labelled as Cold Extracted, while only a physically pressed olive oil may be labelled as Cold Pressed. In many parts of the world, such as Australia, producers using centrifugal extraction still label their products as Cold Pressed.

First cold pressed means "that the fruit of the olive was crushed exactly one time—i.e., the first press. The cold refers to the temperature range of the fruit at the time it is crushed". In Calabria (Italy) the olives are collected in October. In regions like Tuscany or Liguria, the olives collected in November and ground often at night are too cold to be processed efficiently without heating. The paste is regularly heated above the environmental temperatures, which may be as low as 10–15 °C, to extract the oil efficiently with only physical means. Olives pressed in warm regions like Southern Italy or Northern Africa may be pressed at significantly higher temperatures although not heated. While it is important that the pressing temperatures be as low as possible (generally below 25 °C) there is no international reliable definition of "cold pressed".

Furthermore, there is no "second" press of virgin oil, so the term "first press" means only that the oil was produced in a press vs. other possible methods. PDO and PGI refers to olive oils with "exceptional properties and quality derived from their place of origin as well as from the way of their production". The label may indicate that the oil was bottled or packed in a stated country. This does not necessarily mean that the oil was produced there. The origin of the oil may sometimes be marked elsewhere on the label or it may be a mixture of oils from more than one country.

The U.S. Food and Drug Administration permitted a claim on olive oil labels stating: "Limited and not conclusive scientific evidence suggests that eating about two tablespoons (23 g) of olive oil daily may reduce the risk of coronary heart disease."

There have been allegations, particularly in Italy and Spain, that regulation can be sometimes lax and corrupt. Major shippers are claimed to routinely adulterate olive oil so that only about 40% of olive oil sold as "extra virgin" in Italy actually meets the specification. In some cases, colza oil (Swedish turnip) with added color and flavor has been labeled and sold as olive oil. This extensive fraud prompted the Italian government to mandate a new labeling law in 2007 for companies selling olive oil, under which every bottle of Italian olive oil would have to declare the farm and press on which it was produced, as well as display a precise breakdown of the oils used, for blended oils. In February 2008, however, EU officials took issue with the new law, stating that under EU rules such labeling should be voluntary rather than compulsory. Under EU rules, olive oil may be sold as Italian even if it only contains a small amount of Italian oil.

Extra Virgin olive oil has strict requirements and is checked for "sensory defects" that include: rancid, fusty, musty, winey (vinegary) and muddy sediment. These defects can occur for different reasons. The most common are:

- Raw material (olives) infected or battered
- Inadequate harvest, with contact between the olives and soil

In March 2008, 400 Italian police officers conducted "Operation Golden Oil", arresting 23 people and confiscating 85 farms after an investigation revealed a large-scale scheme to relabel oils from other Mediterranean nations as Italian. In April 2008, another operation impounded seven olive oil plants and arrested 40 people in nine provinces of northern and southern Italy for adding chlorophyll to sunflower and soybean oil, and selling it as extra virgin olive oil, both in Italy and abroad; 25,000 liters of the fake oil were seized and prevented from being exported.

On March 15, 2011, the prosecutor's office in Florence, Italy, working in conjunction with the forestry department, indicted two managers and an of-

ficer of Carapelli, one of the brands of the Spanish company Grupo SOS (which recently changed its name to Deoleo). The charges involved falsified documents and food fraud. Carapelli lawyer Neri Pinucci said the company was not worried about the charges and that "the case is based on an irregularity in the documents."

In February 2012, an international olive oil scam was alleged by Spanish police to have taken place, in which palm, avocado, sunflower and other cheaper oils were passed off as Italian olive oil. Police said the oils were blended in an industrial biodiesel plant and adulterated in a way to hide markers that would have revealed their true nature. The oils were not toxic and posed no health risk, according to a statement by the Guardia Civil. Nineteen people were arrested following the year-long joint probe by the police and Spanish tax authorities, part of what they call Operation Lucerna.

Using tiny print to state the origin of blended oil is used as a legal loophole by manufacturers of adulterated and mixed olive oil. Journalist Tom Mueller has investigated crime and adulteration in the olive oil business, publishing the article "Slippery Business" in New Yorker magazine, followed by the 2011 book Extra Virginity. On 3 January 2016 Bill Whitaker presented a program on CBS News including interviews with Mueller and with Italian authorities. It was reported that in the previous month 5,000 tons of adulterated olive oil had been sold in Italy, and that organized crime was heavily involved—the term "Agrimafia" was used. The point was made by Mueller that the profit margin on adulterated olive oil was three times that of the illegal narcotic drug cocaine. He said that over 50% of olive oil sold in Italy was adulterated, as was 75-80% of that sold in the US. Whitaker reported that 3 samples of "extra virgin olive oil" had been bought in a US supermarket and tested; two of the three samples did not meet the required standard, and one of them—with a top-selling US brand—was exceptionally poor.

Molecular Nutrition And Food Research • July 2016

Polyphenol rich olive oils improve lipoprotein particle atherogenic ratios and subclasses profile: A randomized, crossover, controlled trial

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Abstract

SCOPE

Lipoprotein particle measures performed by nuclear magnetic resonance (NMR), and associated ratios, may be better markers for atherosclerosis risk than conventional lipid measures. The effect of two functional olive oils, one enriched with its polyphenols (FVOO, 500 ppm), and the other (FVOOT) with them (250 ppm) and those of thyme (250 ppm), versus a standard virgin olive oil (VOO), on lipoprotein particle atherogenic ratios and subclasses profiles was assessed.

METHODS AND RESULTS

In a randomized, double-blind, crossover, controlled trial, 33 hypercholesterolemic individuals received 25 mL/day of VOO, FVOO, and FVOOT. Intervention periods were of 3 weeks separated by 2-week washout periods. Lipoprotein particle counts and subclasses were measured by NMR. Polyphenols from olive oil and thyme modified the lipoprotein subclasses profile and decreased the total LDL particle/total HDL particle (HDL-P), small HDL/large HDL, and HDL-cholesterol/HDL-P ratios, and decreased the lipoprotein insulin resistance index (LP-IR) ($p < 0.05$).

CONCLUSION

Olive oil polyphenols, and those from thyme provided benefits on lipoprotein particle atherogenic ratios and subclasses profile distribution. Polyphenol-enriched olive oil is a way of increasing the olive oil healthy properties while consuming the same amount of fat, as well as a useful and complementary tool for the management of cardiovascular risk individuals.

http://www.ncbi.nlm.nih.gov/pubmed/26992050

“Using Pharmaexpert, a tool that analyzes the PASS [Prediction of Activity Spectra for Substances]-predicted Biological Activity Spectra of substances based on thousands of “mechanism-effect” and “effect-mechanism” relationships, we illuminate hypothesis-generating pharmacological effects, mechanisms of action, and targets that might **underlie the anti-aging/anti-cancer activities of the gerosuppressant Extra Virgin Olive Oil oleuropeins.**”

Aging • September 2014

Computer-aided discovery of biological activity spectra for anti-aging and anti-cancer olive oil oleuropeins

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Abstract

Aging is associated with common conditions, including cancer, diabetes, cardiovascular disease, and Alzheimer’s disease. The type of multi-targeted pharmacological approach necessary to address a complex multifaceted disease such as aging might take advantage of pleiotropic natural polyphenols affecting a wide variety of biological processes. We have recently postulated that the secoiridoids oleuropein aglycone (OA) and decarboxymethyl oleuropein aglycone (DOA), two complex polyphenols present in health-promoting extra virgin olive oil (EVOO), might constitute a new family of plant-produced gerosuppressant agents. This paper describes an analysis of the biological activity spectra (BAS) of OA and DOA using PASS (Prediction of Activity Spectra for Substances) software. PASS can predict thousands of biological activities, as the BAS of a compound is an intrinsic property that is largely dependent on the compound’s structure and reflects pharmacological effects, physiological and biochemical mechanisms of action, and specific toxicities. Using Pharmaexpert, a tool that analyzes the PASS-predicted BAS of substances based on thousands of “mechanism-effect” and “effect-mechanism” relationships, we illuminate hypothesis-generating pharmacological effects, mechanisms of action, and targets that might underlie the anti-aging/anti-cancer activities of the gerosuppressant EVOO oleuropeins.

Full text, graphs, charts and 72 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4221918/

“This is the first study demonstrating the ability of Olive Oil Phenols to prevent the DNA damage induced by alkene epoxides **providing additional information about the chemopreventive properties of olive oil.**”

Nutritional Cancer • October 2014

Preventive activity of olive oil phenolic compounds on alkene epoxides induced oxidative DNA damage on human peripheral blood mononuclear cells

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Abstract

The aim of this study was to investigate the ability of epoxides of styrene (styrene-7,8-oxide; SO) and 1,3-butadiene (3,4-epoxy-1-butene; 1,2:3,4:-diepoxybutane) to cause oxidative stress and oxidative DNA damage on human peripheral blood mononuclear cells (PBMCs) and whether a complex mixture of olive oil phenols (OOPE) could prevent these effects. The DNA damage was measured by the single-cell gel electrophoresis (SCGE; comet assay). We found that the DNA damage induced by alkene epoxides could be prevented by N-acetyl-cysteine (10 mM) and catalase (100 U/ml). Alkene epoxides caused a significant ($P < 0.05$) increase of both peroxide concentration in extra- and intracellular environment and formamidopyrimidine DNA glycosylase (FPG)- and Endonuclease III (ENDO III)-sensitive sites in PBMCs, demonstrating the presence of oxidized bases. OOPE (1 µg of total phenols/ml) was able to prevent the alkene epoxide induced DNA damage both after 2 and 24 h of incubation. In addition, OOPE completely inhibited the SO-induced intracellular peroxide accumulation in PBMCs and prevented the oxidative DNA damage induced by SO, as evidenced by the disappearance of both FPG- and ENDO III-sensitive sites. This is the first study demonstrating the ability of OOPE to prevent the DNA damage induced by alkene epoxides providing additional information about the chemopreventive properties of olive oil.

http://www.ncbi.nlm.nih.gov/pubmed/25299479

“Over the last few decades, multiple biological properties, **providing antioxidant, anti-inflammatory, chemopreventive and anti-cancer benefits**, as well as the characteristic pungent and bitter taste, have been attributed to Extra Virgin Olive Oil (EVOO) phenols.”

Antioxidants (Basel) • December 2013

Biological Activities of Phenolic Compounds of Extra Virgin Olive Oil

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Abstract

Over the last few decades, multiple biological properties, providing antioxidant, anti-inflammatory, chemopreventive and anti-cancer benefits, as well as the characteristic pungent and bitter taste, have been attributed to Extra Virgin Olive Oil (EVOO) phenols. In particular, growing efforts have been devoted to the study of the antioxidants of EVOO, due to their importance from health, biological and sensory points of view. Hydrophilic and lipophilic phenols represent the main antioxidants of EVOO, and they include a large variety of compounds. Among them, the most concentrated phenols are lignans and secoiridoids, with the latter found exclusively in the Oleaceae family, of which the drupe is the only edible fruit. In recent years, therefore, we have tackled the study of the main properties of phenols, including the relationships between their biological activity and the related chemical structure. This review, in fact, focuses on the phenolic compounds of EVOO, and, in particular, on their biological properties, sensory aspects and antioxidant capacity, with a particular emphasis on the extension of the product shelf-life.

Full text, graphs,charts and 122 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4665453/

Rejuvenation Research • February 2012

Phenolic secoiridoids in extra virgin olive oil impede fibrogenic and oncogenic epithelial-to-mesenchymal transition: extra virgin olive oil as a source of novel antiaging phytochemicals

Author information

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Abstract

The epithelial-to-mesenchymal transition (EMT) genetic program is a molecular convergence point in the life-threatening progression of organ fibrosis and cancer toward organ failure and metastasis, respectively. Here, we employed the EMT process as a functional screen for testing crude natural extracts for accelerated drug development in fibrosis and cancer. Because extra virgin olive oil (EVOO) (i.e., the juice derived from the first cold pressing of the olives without any further refining process) naturally contains high levels of phenolic compounds associated with the health benefits derived from consuming an EVOO-rich Mediterranean diet, we have tested the ability of an EVOO-derived crude phenolic extract to regulate fibrogenic and oncogenic EMT in vitro. High-performance liquid chromatography (HPLC) coupled to time-of-flight (TOF) mass spectrometry assays revealed that the EVOO phenolic extract was mainly composed (~70%) of two members of the secoiridoid family of complex polyphenols, namely oleuropein aglycone-the bitter principle of olives-and its derivative decarboxymethyl oleuropein aglycone. EVOO secoiridoids efficiently prevented loss of proteins associated with polarized epithelial phenotype (i.e., E-cadherin) as well as de novo synthesis of proteins associated with mesenchymal migratory morphology of transitioning cells (i.e., vimentin). The ability of EVOO to impede transforming growth factor-ß (TGF-ß)-induced disintegration of E-cadherin-mediated cell-cell contacts apparently occurred as a consequence of the ability of EVOO phenolics to prevent the upregulation of SMAD4-a critical mediator of TGF-ß signaling-and of the SMAD transcriptional cofactor SNAIL2 (Slug)-a well-recognized epithelial repressor. Indeed, EVOO phenolics efficiently prevented crucial TGF-ß-induced EMT transcriptional events, including upregulation of SNAI2, TCF4, VIM (Vimentin), FN (fibronectin), and SERPINE1 genes. While awaiting a better mechanistic understanding of how EVOO phenolics molecularly shut down the EMT differentiation process, it seems reasonable to suggest that nontoxic Oleaceae secoiridoids certainly merit to be considered for aging studies and, perhaps, for ulterior design of more pharmacologically active second-generation anti-EMT molecules.

Full text, graphs, charts, photos and 118 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283896/

“Extra Virgin Olive Oil-derived lignans and secoiridoids might provide an excellent and safe platform for the design of new HER2 targeted **anti-breast cancer drugs.”**

International Journal Of Oncology • January 2009

Extra-virgin olive oil polyphenols inhibit HER2 (erbB-2)-induced malignant transformation in human breast epithelial cells: relationship between the chemical structures of extra-virgin olive oil secoiridoids and lignans and their inhibitory activities on the tyrosine kinase activity of HER2

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Abstract

Depending on their structure, some polyphenols (e.g. flavonoids) abundantly found in plant-derived beverages such as green tea can efficiently inhibit tyrosine kinase and serine/threonine kinase activities. Extra-virgin olive oil (EVOO - the juice of the olive obtained solely by pressing and consumed without any further refining process) is unique among other vegetable oils because of the high level of naturally occurring phenolic compounds. We explored the ability of EVOO polyphenols to modulate HER2 tyrosine kinase receptor-induced in vitro transformed phenotype in human breast epithelial cells. Using MCF10A normal breast epithelial cells retrovirally engineered to overexpress the wild-type sequence of human HER2, we further determined the relationship between chemical structures of EVOO-derived phenolics and their inhibitory activities on the tyrosine kinase activity of the HER2 oncoprotein. When the activation (phosphorylation) status of HER2 was semi-quantitatively measured the secoiridoids blocked HER2 signaling by rapidly reducing the activation status of the 1248 tyrosine residue (Y1248), the main autophosphorylation site of HER2. EVOO-derived single phenols tyrosol and hydroxytyrosol and the phenolic acid elenolic acid failed to significantly decrease HER2 tyrosine kinase activity. The anti-HER2 tyrosine kinase activity IC50 values were up to 5-times lower in the presence of EVOO-derived lignans and secoiridoids than in the presence of EVOO-derived single phenols and phenolic acids. EVOO polyphenols induced strong tumoricidal effects by selectively triggering high levels of apoptotic cell death in HER2-positive MCF10A/HER2 cells but not in MCF10A/pBABE matched control cells. EVOO lignans and secoiridoids prevented HER2-induced in vitro transformed phenotype as they inhibited colony formation of MCF10A/HER2 cells in soft-agar. Our current findings not only molecularly support recent epidemiological evidence revealing that EVOO-related anti-breast cancer effects primarily affect the occurrence of breast tumors over-expressing the type I receptor tyrosine kinase HER2 but further suggest that the stereochemistry of EVOO-derived lignans and secoiridoids might provide an excellent and safe platform for the design of new HER2 targeted anti-breast cancer drugs.

http://www.ncbi.nlm.nih.gov/pubmed/19082476

“Overall, these results suggest that Olive Oil-Phenols ...
may efficiently prevent the initiation step of carcinogenesis in vivo,
because the concentrations effective against the oxidative DNA damage
could be easily reached with normal intake of olive oil.”

Journal Nutrition • August 2008

Oxidative DNA damage is prevented by extracts of olive oil, hydroxytyrosol, and other olive phenolic compounds in human blood mononuclear cells and HL60 cells

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Abstract

Our aim in this study was to provide further support to the hypothesis that phenolic compounds may play an important role in the anticarcinogenic properties of olive oil. We measured the effect of olive oil phenols on hydrogen peroxide (H(2)O(2))-induced DNA damage in human peripheral blood mononuclear cells (PBMC) and promyelocytic leukemia cells (HL60) using single-cell gel electrophoresis (comet assay). Hydroxytyrosol [3,4-dyhydroxyphenyl-ethanol (3,4-DHPEA)] and a complex mixture of phenols extracted from both virgin olive oil (OO-PE) and olive mill wastewater (WW-PE) reduced the DNA damage at concentrations as low as 1 micromol/L when coincubated in the medium with H(2)O(2) (40 micromol/L). At 10 micromol/L 3,4-DHPEA, the protection was 93% in HL60 and 89% in PBMC. A similar protective activity was also shown by the dialdehydic form of elenoic acid linked to hydroxytyrosol (3,4-DHPEA-EDA) on both kinds of cells. Other purified compounds such as isomer of oleuropein aglycon (3,4-DHPEA-EA), oleuropein, tyrosol, [p-hydroxyphenyl-ethanol (p-HPEA)] the dialdehydic form of elenoic acid linked to tyrosol, caffeic acid, and verbascoside also protected the cells against H(2)O(2)-induced DNA damage although with a lower efficacy (range of protection, 25-75%). On the other hand, when tested in a model system in which the oxidative stress was induced by phorbole 12-myristate 13-acetate-activated monocytes, p-HPEA was more effective than 3,4-DHPEA in preventing the oxidative DNA damage. Overall, these results suggest that OO-PE and WW-PE may efficiently prevent the initiation step of carcinogenesis in vivo, because the concentrations effective against the oxidative DNA damage could be easily reached with normal intake of olive oil.

http://www.ncbi.nlm.nih.gov/pubmed/18641183

“Treatment with PE [virgin olive oil phenol extract] induced a differentiation in HL60 cells, which subsequently acquired the ability to produce superoxide ions and reduce nitroblue tetrazolium to formazan. These results support the hypothesis that **polyphenols play a critical role in the anticancer activity of olive oil**.”

Journal Of Nutrition • March 2006

Virgin olive oil phenols inhibit proliferation of human promyelocytic leukemia cells (HL60) by inducing apoptosis and differentiation

Author information

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Abstract

Although epidemiologic evidence and animal studies suggest that olive oil may prevent the onset of cancer, the components responsible for such an effect and their mechanisms of action remain largely unknown. In the present study, we investigated the effect of a virgin olive oil phenol extract (PE) on proliferation, the cell cycle distribution profile, apoptosis, and differentiation of the human promyelocytic cell line HL60. PE inhibited HL60 cell proliferation in a time- and concentration-dependent manner, as demonstrated by the viable cell count and 3-[4,5-dimethyl(thiazol-2-yl)]-3,5-diphenyltetrazolium bromide (MTT) metabolism. Cell growth was completely blocked at a PE concentration of 13.5 mg/L; apoptosis was also induced as detected by fluorescence microscopy and flow cytometry. Determination of the cell cycle distribution by flow cytometry revealed an accumulation of cells in the G(0)/G(1) phase. Two compounds isolated from PE, the dialdehydic forms of elenoic acid linked to hydroxytyrosol (3,4-DHPEA-EDA) and to tyrosol (pHPEA-EDA), were shown to possess properties similar to those of PE; they account for a part of the powerful effects exerted by the complex mixture of compounds present in PE. The concentrations of the different compounds in PE were determined by HPLC, and the purity of 3,4-DHPEA-EDA and pHPEA-EDA was ascertained by NMR. Treatment with PE induced a differentiation in HL60 cells, which subsequently acquired the ability to produce superoxide ions and reduce nitroblue tetrazolium to formazan. These results support the hypothesis that polyphenols play a critical role in the anticancer activity of olive oil.

http://www.ncbi.nlm.nih.gov/pubmed/16484533

“We recently hypothesized that a novel molecular explanation concerning the anti-cancer actions of olive oil may relate to the ability of its monounsaturated fatty acid (MUFA) oleic acid (OA; 18:1n-9) **to specifically regulate cancer-related oncogenes**. Supporting our hypothesis, exogenous supplementation of cultured breast cancer cells with physiological concentrations of Oleic Acid was found to suppress the overexpression of HER2 (Her-2/neu, erbB-2), a well-characterized oncogene **playing a key role in the etiology, progression and response to chemotherapy and endocrine therapy in approximately 20% of breast carcinomas**.”

Clinical Translational Oncology • January 2006

Mediterranean diet, olive oil and cancers

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Abstract

Olive oil is an integral ingredient of the “Mediterranean diet” and accumulating evidence suggests that it may have a potential role in lowering the risk of several types of cancers. The mechanisms by which the cancer-preventing effects of olive oil can be performed, however, are not known. We recently hypothesized that a novel molecular explanation concerning the anti-cancer actions of olive oil may relate to the ability of its monounsaturated fatty acid (MUFA) oleic acid (OA; 18:1n-9) to specifically regulate cancer-related oncogenes. Supporting our hypothesis, exogenous supplementation of cultured breast cancer cells with physiological concentrations of OA was found to suppress the overexpression of HER2 (Her-2/neu, erbB-2), a well-characterized oncogene playing a key role in the etiology, progression and response to chemotherapy and endocrine therapy in approximately 20% of breast carcinomas. OA treatment was also found to synergistically enhance the efficacy of trastuzumab, a humanized monoclonal antibody binding with high affinity to the ectodomain (ECD) of the Her2-coded p185(HER2) oncoprotein. Moreover, OA exposure significantly diminished the proteolytic cleavage of the ECD of HER2 and, consequently, its activation status, a crucial molecular event that determines both the aggressive behavior and the response to trastuzumab of Her2-overexpressing breast carcinomas. Our most recent findings further reveal that OA exposure may suppresses HER2 at the transcriptional level by up-regulating the expression of the Ets protein PEA3 -a DNA-binding protein that specifically blocks HER2 promoter activity- in breast, ovarian and stomach cancer cell lines. This anti-HER2 property of OA offers a previously unrecognized molecular mechanism by which olive oil may regulate the malignant behavior of cancer cells. From a clinical perspective, it could provide an effective means of influencing the outcome of Her-2/neu-overexpressing human carcinomas with poor prognosis. Indeed, OA-induced transcriptional repression of HER2 oncogene may represent a novel genomic explanation linking “Mediterranean diet”, olive oil and cancer as it seems to equally operate in various types of Her-2/neu-related carcinomas.

http://www.ncbi.nlm.nih.gov/pubmed/16632435

“Gene repression was seen in tumour-derived cell lines with Her-2/neu gene amplification and overexpression, including SK-Br3 (56% reduction), SK-OV3 (75% reduction) and NCI-N87 (55% reduction) **breast, ovarian and stomach cancer cell lines, respectively.**”

European Journal Of Cancer • October 2006

A genomic explanation connecting “Mediterranean diet”, olive oil and cancer: oleic acid, the main monounsaturated fatty acid of olive oil, induces formation of inhibitory “PEA3 transcription factor-PEA3 DNA binding site” complexes at the Her-2/neu (erbB-2) oncogene promoter in breast, ovarian and stomach cancer cells

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Abstract

Olive oil is an integral ingredient of the “Mediterranean diet” and accumulating evidence suggests that it may have a potential role in lowering risk of several cancers. We recently hypothesized that the anti-cancer actions of olive oil may relate to its monounsaturated fatty acid (MUFA) oleic acid (OA; 18:1n-9) content to specifically regulate oncogenes. In this study, transient transfection experiments with human Her-2/neu promoter-driven luciferase gene established the ability of OA to specifically repress the transcriptional activity of Her-2/neu gene. Gene repression was seen in tumour-derived cell lines with Her-2/neu gene amplification and overexpression, including SK-Br3 (56% reduction), SK-OV3 (75% reduction) and NCI-N87 (55% reduction) breast, ovarian and stomach cancer cell lines, respectively. Also marginal decreases in promoter activity were observed in cancer cells expressing physiological levels of Her-2/neu (20% reduction in MCF-7 breast cancer cells). Remarkably, OA treatment in Her-2/neu-overexpressing cancer cells was found to induce up-regulation of the Ets protein polyomavirus enhancer activator 3 (PEA3), a transcriptional repressor of Her-2/neu promoter. Also, an intact PEA3 DNA-binding-site at endogenous Her-2/neu gene promoter was essential for OA-induced repression of this gene. Moreover, OA treatment failed to decrease Her-2/neu protein levels in MCF-7/Her2-18 transfectants, which stably express full-length human Her-2/neu cDNA controlled by a SV40 viral promoter. OA-induced transcriptional repression of Her-2/neu through the action of PEA3 protein at the promoter level may represent a novel mechanism linking “Mediterranean diet” and cancer.

http://www.ncbi.nlm.nih.gov/pubmed/16406575

“A recent discovery that dietary fatty acids can interact with the human genome by regulating the amount and/or activity of transcription factors has opened a whole new line of research aimed to molecularly corroborate the anti-cancer benefits of the olive oil-based Mediterranean diet and the underlying mechanisms. Our most recent findings reveal that oleic acid (OA; 18:1n-9), the main olive oil’s monounsaturated fatty acid, can suppress the overexpression of HER2 (erbB-2), a well-characterized oncogene **playing a key role in the etiology, invasive progression and metastasis in several human cancers.**”

Currents In Pharmacology And Biotechnology • December 2006

Mediterranean dietary traditions for the molecular treatment of human cancer: anti-oncogenic actions of the main olive oil’s monounsaturated fatty acid oleic acid (18:1n-9)

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Abstract

The final proof about the specific mechanisms by which the different components of olive oil, the principal source of fat in a typical “Mediterranean diet”, exert their potential protective effects on the promotion and progression of several human cancers requires further investigations. A recent discovery that dietary fatty acids can interact with the human genome by regulating the amount and/or activity of transcription factors has opened a whole new line of research aimed to molecularly corroborate the ant-cancer benefits of the olive oil-based Mediterranean diet and the underlying mechanisms. Our most recent findings reveal that oleic acid (OA; 18:1n-9), the main olive oil’s monounsaturated fatty acid, can suppress the overexpression of HER2 (erbB-2), a well-characterized oncogene playing a key role in the etiology, invasive progression and metastasis in several human cancers. First, exogenous supplementation with physiological concentrations of OA significantly down-regulates HER2-coded p185(Her-2/neu) oncoprotein in human cancer cells naturally harboring amplification of the HER gene. Second, OA exposure specifically represses the transcriptional activity of the human HER2 gene promoter in tumor-derived cell lines naturally exhibiting HER2 gene amplification and p185(Her-2/neu) protein overexpression but not in cancer cells expressing physiological levels of HER2. Third, OA treatment induces the up-regulation of the Ets protein PEA3 (a transcriptional repressor of the HER2 gene promoter) solely in cancer cells naturally displaying HER2 gene amplification. Fourth, HER2 gene promoter bearing a PEA3 site-mutated sequence cannot be negatively regulated by OA, while treatment with OA fails to repress the expression of a human full-length HER2 cDNA controlled by a SV40 viral promoter. Fifth, OA-induced inhibition of HER2 promoter activity does not occur if HER2 gene-amplified cancer cells do no concomitantly exhibit high levels of Fatty Acid Synthase (FASN; Oncogenic antigen-519) as specific depletion of FASN, which itself similarly suppresses HER2 overexpression by inducing PEA3-dependent repression of HER2 gene promoter, strongly antagonizes the inhibitory effects of OA on HER2 gene promoter activity. Considering that OA treatment efficiently blocks FASN activity and down-regulates FASN protein expression, it is reasonable to suggest that an accumulation of supra-physiological concentrations of the FASN substrate malonyl-CoA, due to its reduced utilization by FASN in the presence of exogenous OA, appears to act as an indicator of “cell fuel” availability capable to suppress HER2 expression via formation of inhibitory “PEA3 protein-PEA3 DNA binding site” complexes on the endogenous HER2 promoter. Indeed, malonyl-CoA on its own dramatically decreases HER2 promoter activity, while OA or malonyl-CoA similarly up-regulates PEA3 gene promoter activity. This previously unrecognized ability of OA to directly affect the expression of a cluster of interrelated human cancer genes (i.e., HER2, FASN and PEA3) should open a new line of research aimed to explore the anti-cancer effects of OA. Certainly, an appropriate dietary intervention reproducing this prominent anti-oncogenic feature of the “Mediterranean diet” must be carried out in animal models and human pilot studies in the future. Only then we will know whether the old “Mediterranean dietary traditions” will become a new molecular approach in the management of cancer disease.

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Annals In Oncology • March 2005

Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu (erbB-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab (Herceptin) in breast cancer cells with Her-2/neu oncogene amplification

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ABSTRACT

The relationship between the intake of olive oil, the richest dietary source of the monounsaturated fatty acid oleic acid (OA; 18:1n-9), and breast cancer risk and progression has become a controversial issue. Moreover, it has been suggested that the protective effects of olive oil against breast cancer may be due to some other components of the oil rather than to a direct effect of OA.

METHODS

Using flow cytometry, western blotting, immunofluorescence microscopy, metabolic status (MTT), soft-agar colony formation, enzymatic in situ labeling of apoptosis-induced DNA double-strand breaks (TUNEL assay analyses), and caspase-3-dependent poly-ADP ribose polymerase (PARP) cleavage assays, we characterized the effects of exogenous supplementation with OA on the expression of Her-2/neu oncogene, which plays an active role in breast cancer etiology and progression. In addition, we investigated the effects of OA on the efficacy of trastuzumab (Herceptin), a humanized monoclonal antibody binding with high affinity to the ectodomain of the Her-2/neu-coded p185(Her-2/neu) oncoprotein. To study these issues we used BT-474 and SKBr-3 breast cancer cells, which naturally exhibit amplification of the Her-2/neu oncogene.

RESULTS

Flow cytometric analyses demonstrated a dramatic (up to 46%) reduction of cell surface-associated p185(Her-2/neu) following treatment of the Her-2/neu-overexpressors BT-474 and SK-Br3 with OA. Indeed, this effect was comparable to that found following exposure to optimal concentrations of trastuzumab (up to 48% reduction with 20 microg/ml trastuzumab). Remarkably, the concurrent exposure to OA and suboptimal concentrations of trastuzumab (5 microg/ml) synergistically down-regulated Her-2/neu expression, as determined by flow cytometry (up to 70% reduction), immunoblotting, and immunofluorescence microscopy studies. The nature of the cytotoxic interaction between OA and trastuzumab revealed a strong synergism, as assessed by MTT-based cell viability and anchorage-independent soft-agar colony formation assays. Moreover, OA co-exposure synergistically enhanced trastuzumab efficacy towards Her-2/neu overexpressors by promoting DNA fragmentation associated with apoptotic cell death, as confirmed by TUNEL and caspase-3-dependent PARP cleavage. In addition, treatment with OA and trastuzumab dramatically increased both the expression and the nuclear accumulation of p27(Kip1), a cyclin-dependent kinase inhibitor playing a key role in the onset and progression of Her-2/neu-related breast cancer. Finally, OA co-exposure significantly enhanced the ability of trastuzumab to inhibit signaling pathways downstream of Her-2/neu, including phosphoproteins such as AKT and MAPK.

CONCLUSIONS

These findings demonstrate that OA, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu overexpression, which, in turn, interacts synergistically with anti-Her-2/neu immunotherapy by promoting apoptotic cell death of breast cancer cells with Her-2/neu oncogene amplification. This previously unrecognized property of OA offers a novel molecular mechanism by which individual fatty acids may regulate the malignant behavior of breast cancer cells and therefore be helpful in the design of future epidemiological studies and, eventually, dietary counseling.

Full text, graphs, charts and 62 references

http://annonc.oxfordjournals.org/content/16/3/359.full.pdf+htmlygytiyr

“In conclusion, **cytoprotective as well as cytotoxic compounds with potential pharmaceutical properties were detected in extracts from olive oil** related sources by using the comet assay methodology.”

Free Radical Research • July 2005

DNA protecting and genotoxic effects of olive oil related components in cells exposed to hydrogen peroxide

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Abstract

In search for compounds, able to protect nuclear DNA in cells exposed to oxidative stress, extracts from olive leaves, olive fruits, olive oil and olive mill waste water were tested by using the “single cell gel electrophoresis” methodology (comet assay). Jurkat cells in culture were exposed to continuously generated hydrogen peroxide (11.8+/-1.5 microM per min) by direct addition into the growth medium of the appropriate amount of the enzyme “glucose oxidase” in the presence or absence of the tested total extracts. The protective effects of the tested extracts or isolated compounds were evaluated from their ability to decrease hydrogen peroxide-induced formation of single strand breaks in the nuclear DNA, while the toxic effects were estimated from the increase of DNA damage when the extracts or isolated compounds were incubated directly with the cells. Significant protection was observed in extracts from olive oil and olive mill waste water. However, above a concentration of 100 microg/ml olive oil extracts exerted DNA damaging effects by themselves in the absence of any H2O2. Extracts from olive leaves and olive fruits although protective, were also able to induce DNA damage by themselves. Main compounds isolated from the above described total extracts, like oleuropein glucoside, tyrosol, hydroxytyrosol and caffeic acid, were tested in the same experimental system and found to exert cytotoxic (oleuropein glucoside), no effect (tyrosol) or protective effects (hydroxytyrosol and caffeic acid). In conclusion, cytoprotective as well as cytotoxic compounds with potential pharmaceutical properties were detected in extracts from olive oil related sources by using the comet assay methodology.

http://www.ncbi.nlm.nih.gov/pubmed/16036359

CHAPTER SIXTEEN

Butylated Hydroxyanisole (BHA) & Butylated Hydroxytoluene (BHT)

The Peer Review

BHA retards rancidity in fats, oils, and oil-containing foods. While some studies indicate it is safe, other studies demonstrate that it causes cancer in rats, mice, and hamsters. Those cancers are controversial because they occur in the forestomach, an organ that humans do not have. However, a chemical that causes cancer in at least one organ in three different species indicates that it might be carcinogenic in humans. That is why the U.S. Department of Health and Human Services considers BHA to be "reasonably anticipated to be a human carcinogen." Nevertheless, the Food and Drug Administration still permits BHA to be used in foods.

This synthetic chemical can be replaced by safer chemicals (e.g., vitamin E), safer processes (e.g., packing foods under nitrogen instead of air), or can simply be left out (many brands of oily foods, such as potato chips, don't use an antioxidant).

BHT retards rancidity in oils. It either increased or decreased the risk of cancer in various animal studies. Residues of BHT occur in human fat. BHT is unnecessary or is easily replaced by safe substitutes. Avoid it when possible.

These two drugs are used primarily in cereal, chewing gum, potato chips and vegetable oil but can be found in any foods that contain fat that needs to be preserved for a long period of time.

Butylated hydroxyanisole (BHA) is a preservative that affects the neurological system of your brain, alters behavior, and has the potential to cause cancer. It can be found in breakfast cereal, nut mixes, chewing gum, butter spread, meat, dehydrated potatoes, popcorn, chips, and beer, just to name a few.

BHA is known to cause cancer in rats, and may be a cancer-causing agent in humans as well. According to the US Department of Health and Human Services, National Toxicology Program's 2011 Report on Carcinogens, BHA "is reasonably anticipated to be a human carcinogen."

The international cancer agency categorizes it as a possible human carcinogen, and it's listed as a known carcinogen under California's Proposition 65.

BHA may also trigger allergic reactions and hyperactivity. BHA is banned from infant foods in the UK and is banned from use in all foods in certain parts of the EU and Japan. In the US, the FDA considers BHA to be a GRAS additive.

BHT is chemically similar to BHA and the two preservatives are often used together. While BHT is not considered a carcinogen like BHA, it has been linked to tumor development in animals.

It's also been linked to developmental effects and thyroid changes in animal studies, which suggests it may be an endocrine-disrupting chemical. In the US, BHT is given GRAS status. Both chemicals should be avoided.

Butylated Hydroxyanisole

CAS No. 25013-16-5

Reasonably anticipated to be a human carcinogen
First listed in the Sixth Annual Report on Carcinogens (1991) Also known as BHA or (1,1-dimethylethyl)-4-methoxyphenol)

Food-grade BHA contains over 85% 3-BHA and less than 15% 2-BHA, while cosmetic-grade BHA contains 90% 3-BHA and 8% 2-BHA. Since 1947, BHA has been added to edible fats and fat-containing foods for its antioxidant properties. It is also used in foods cooked or fried in animal oils, because of its high thermal stability and its ability to remain active in baked and fried foods (HSDB 2009). BHA is added to butter, lard, meats, cereals, baked goods, sweets, beer, vegetable oils, potato chips, snack foods, nuts and nut products, dehydrated potatoes, and flavoring agents. It is used in sausage, poultry and meat products, dry mixes for beverages and desserts, glazed fruits, chewing gum, active dry yeast, de-foaming agents for beet sugar and yeast, and emulsion stabilizers for shortening (IARC 1986). BHA stabilizes the petroleum wax coatings of food packaging (HSDB 2009). BHA is considered by the U.S. Food and Drug Administration (FDA) to be generally recognized as safe (GRAS) when the antioxidant content does not exceed 0.02% by weight of the food's total fat or oil content.

BHA is one of the primary antioxidants used in feeds, because it retards the oxidation of vitamin A, fats, and vegetable oils. It is an effective stabilizer for essential oils, para n, and polyethylenes (HSDB 2009). It is used as an antioxidizing agent in a biomaterial made from polyurethane and polyethylene oxide used to make mainline catheters (Silverstein et al. 1997). BHA is used as a preservative and antioxidant in pharmaceutical preparations and cosmetic formulations containing fats and oils. A 1981 FDA survey found that BHA was used in 3,217 of 21,279 cosmetic formulations; the majority (88%) of the reported concentrations did not exceed 0.1%. In that survey, use of BHA was highest in lipstick formulations (1,256 products), followed by eyeshadow products (410) (IARC 1986). For industrial use, BHA has largely been replaced by tert-butylhydroquinone.

PRODUCTION

In 2009, no producers of BHA were identified worldwide (SRI 2009), but it was available from 46 suppliers, including 18 U.S. suppliers (ChemSources 2009). No recent data on U.S. imports or exports of BHA were found. Reports led under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of BHA totaled 10,000 to 500,000 lb in 1986 and 2000, 1 million to 10 million pounds in 1996, and less than 500,000 lb in 2006 (EPA 2004, 2009).

EXPOSURE

Routes of human exposure to BHA are ingestion, inhalation, and dermal contact. In 1975, the estimated average daily intake of BHA in the diet was 4.3 mg (IARC 1986). Estimated annual U.S. use of BHA in food increased from 170,000 kg (374,000 lb) in 1960 to 300,000 kg (660,000 lb) between 1970 and 1982 (IARC 1986). Total reported annual use of BHA in the mid 1970s was 450 metric tons (990,000 lb) (Nicholas et al. 1978). The concentration of BHA in six samples of human adipose tissue ranged from 0.01 to 0.03 ppm (Conacher et al. 1986). Dermal exposure to BHA occurs from its use as an antioxidant in cosmetic products, especially lipstick and eye shadow (IARC

1986). BHA is also used as an antioxidant for some rubber and petroleum products, and it is a stabilizer for vitamin A (HSDB 2009).

Workers potentially are exposed to BHA in certain industries, including food producers, animal feed producers, livestock producers, cosmetic manufacturers, some petroleum workers, and rubber producers and those who handle the end products, such as tires. Fast-food service personnel who normally cook and serve fried and oily foods potentially are exposed to BHA at high levels; BHA is volatile at 150°C to 170°C (302°F to 338°F) and is readily lost from thermal processes that generate steam (Warner et al. 1986).

CARCINOGENICITY

Butylated hydroxyanisole (BHA) is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

CANCER STUDIES IN EXPERIMENTAL ANIMALS

Dietary exposure to BHA caused benign and malignant tumors of the forestomach (papilloma and squamous-cell carcinoma) in rats of both sexes and in male mice and hamsters (IARC 1986, Masui et al. 1986). Since BHA was listed in the Sixth Annual Report on Carcinogens, an additional study in experimental animals has been identified. Dietary administration of BHA to hermaphroditic Rivulus marmoratus as larvae caused liver cancer (hepatocellular carcinoma) in the adults (Park et al. 1990).

CANCER STUDIES IN HUMANS

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to BHA. Since BHA was listed in the Sixth Annual Report on Carcinogens, one epidemiological study of BHA has been identified. A population-based nested case-control study of stomach cancer in men and women within the Netherlands Cohort Study of dietary intake found no increase in risk at typical levels of dietary intake of BHA (Botterweck et al. 2000).

PROPERTIES

BHA is an antioxidant which exists at room temperature as a white or slightly yellow, waxy solid with a faint characteristic odor (IARC 1986). BHA in commercial use consists of a mixture of 3-tert-butyl-4- hydroxyanisole (3-BHA) and 2-tert-butyl-4-hydroxyanisole (2-BHA). BHA is insoluble in water, but is soluble in fats, oils, propylene glycol, petroleum ether, chloroform, and 50% alcohol.

USE

BHA is used primarily as an antioxidant and preservative in food, food packaging, animal feed, cosmetics and in rubber.

Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 89,673 workers, including 44,061 women, potentially were exposed to BHA. Most of these workers were in the Health Services (> 24,000 workers), Food (> 18,000 workers), and Chemical and Allied Products industries (> 13,000 workers) (NIOSH 1990).

FDA REGULATIONS

BHA is generally recognized as safe for use in food when the total of antioxidants is not greater than 0.02% of fat or oil content. BHA may be used as a food additive permitted for direct addition to food for human consumption as prescribed in 21 CFR 172 and 166. BHA may be used in the manufacture of food packaging materials, with a limit of addition to food of 0.005%. BHA may be used as an antioxidant in defoaming agents for processed foods, not to exceed 0.1% by weight of defoamer.

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Pharmacology • January 2016

Butylated Hydroxyanisole Potently Inhibits Rat and Human 11ß-Hydroxysteroid Dehydrogenase Type 2

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Abstract

Butylated hydroxyanisole (BHA) is a widely used antioxidant for food preservation. 11ß-hydroxysteroid dehydrogenases, isoforms 1 (HSD11B1) and 2 (HSD11B2) have been demonstrated to be the regulators of the local level of active glucocorticoid, which has a broad range of physiological actions. In this study, the potency of BHA was tested for the inhibition of HSD11B1 and HSD11B2 in rat and human tissues. BHA showed potent inhibition of HSD11B2 with the half maximal inhibitory concentration calculated at 13.99 and 69.25 μmol/l for the rat and human, respectively. Results showed that BHA competitively inhibited HSD11B2 when a steroid substrate was used. However, it served as a mixed inhibition factor when the cofactor NAD+ was used. In contrast, the potency of BHA to inhibit both rat and human HSD11B1 was diminished, with the concentration of 100 μmol/l causing no inhibitory effect on the isoform. **In conclusion, we observed that BHA is a selective inhibitor of HSD11B2, implying that this agent may cause excessive glucocorticoid action in local tissues such as kidney and placentas.**

http://www.ncbi.nlm.nih.gov/pubmed/26565409

Human Experimental Toxicology • April 2016

Antioxidant and nephroprotective potential of butylated hydroxyanisole [BHA] against ferric nitrilotriacetate-induced oxidative stress and early tumor events

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Abstract

The present study was aimed to study protective effect of butylated hydroxyanisole (BHA), a phenolic antioxidant used in foods on ferric nitrilotriacetate (Fe-NTA)-induced nephrotoxicity. Male albino rats of Wistar strain (4-6 weeks old) weighing 125-150 g were used in this study. Animals were given a single dose of Fe-NTA (9 mg kg(-1) body weight) after treatment with BHA (1 and 2 mg animal(-1) day(-1)). Fe-NTA treatment enhanced ornithine decarboxylase (ODC) activity to 5.3-fold, and [(3)H]-thymidine incorporation in DNA to 2.5-fold in kidney compared with the corresponding saline-treated control, whereas glutathione (GSH) levels and the activities of antioxidant enzymes decreased to a range of 2- to 2.5-fold in kidney. These changes were reversed significantly in animals receiving a pretreatment of BHA. The enhanced ODC activity and DNA synthesis showed a reduction to 2.12-fold and 1.15-fold, respectively, at a higher dose of 2 mg BHA day(-1) animal(-1), compared with the Fe-NTA-treated groups. Pretreatment with BHA prior to Fe-NTA treatment increased GSH and the activities of antioxidant enzymes to a range of 1.5- to 2-fold in kidney. The results indicate that BHA suppresses Fe-NTA-induced nephrotoxicity in male Wistar rats.

http://www.ncbi.nlm.nih.gov/pubmed/26078281

“... BHA and BHT proved to be weak anti-androgens ...”

Toxicology In Vitro • April 2016

Individual and combined in vitro (anti)androgenic effects of certain food additives and cosmetic preservatives

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Abstract

The individual and combined (binary mixtures) (anti)androgenic effect of butylparaben (BuPB), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and propyl gallate (PG) was evaluated using the MDA-kb2 cell line. Exposing these cells to AR agonists results in the expression of the reporter gene (encoding for luciferase) and luminescence can be measured in order to monitor the activity of the reporter protein. In case of the evaluation of the anti-androgenic effect, the individual test compounds or binary mixtures were tested in the presence of a fixed concentration of a strong AR agonist (1000pM 5-alpha-dihydrotestosterone; DHT). Cell viability was assessed using a resazurin based assay. For PG, this is the first report in the literature concerning its (anti)androgenic activity. In case of both individual and mixture testing none of the compounds or binary combinations showed androgenic activity. When tested in the presence of DHT, BuPB, BHA and BHT proved to be weak anti-androgens and this was confirmed during the evaluation of binary mixtures (BuPB+BHA, BuPB+BHT and BHA+BHT). Besides performing the in vitro testing of the binary combinations, two mathematical models (dose addition and response addition) were evaluated in terms of accuracy of prediction of the anti-androgenic effect of the selected binary mixtures. The dose addition model guaranteed a good correlation between the experimental and predicted data. However, no estimation was possible in case of mixtures containing PG, due to the lack of effect of the compound in case of the individual testing.

http://www.ncbi.nlm.nih.gov/pubmed/26812027

“These results suggest that refinement of exposure, based on the assessment of food levels, is needed to estimate the exposure of children to BHA and benzoates for which the risk of exceeding the Acceptable Daily Intake cannot be excluded when using occurrence data.”

Food Additive Contamination Part A
Chemistry, Analysis, Control, Exposure And Risk Assessment • February 2015

Dietary exposure to benzoates (E210-E213), parabens (E214-E219), nitrites (E249-E250), nitrates (E251-E252), **BHA** (E320), **BHT** (E321) and aspartame (E951) in children less than 3 years old in France

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Abstract

This study aimed to estimate the exposure to seven additives (benzoates, parabens, nitrites, nitrates, BHA, BHT and aspartame) in children aged less than 3 years old in France. A conservative approach, combining individual consumption data with maximum permitted levels, was carried out for all the additives. More refined estimates using occurrence data obtained from products' labels (collected by the French Observatory of Food Quality) were conducted for those additives that exceeded the acceptable daily intake (ADI). Information on additives' occurrence was obtained from the food labels. When the ADI was still exceeded, the exposure estimate was further refined using measured concentration data, if available. When using the maximum permitted level (MPL), the ADI was exceeded for benzoates (1.94 mg kg(-1) bw day(-1)), nitrites (0.09 mg kg(-1) bw day(-1)) and BHA (0.39 mg kg(-1) bw day(-1)) in 25%, 54% and 20% of the entire study population respectively. The main food contributors identified with this approach were current foods as these additives are not authorised in specific infant food: vegetable soups and broths for both benzoates and BHA, delicatessen and meat for nitrites. The exposure estimate was significantly reduced when using occurrence data, but in the upper-bound scenario the ADI was still exceeded significantly by the age group 13-36 months for benzoates (2%) and BHA (1%), and by the age group 7-12 months (16%) and 13-36 months (58%) for nitrites. Measured concentration data were available exclusively for nitrites and the results obtained using these data showed that the nitrites' intake was below the ADI for all the population considered in this study. These results suggest that refinement of exposure, based on the assessment of food levels, is needed to estimate the exposure of children to BHA and benzoates for which the risk of exceeding the ADI cannot be excluded when using occurrence data.

http://www.ncbi.nlm.nih.gov/pubmed/25686474

“The combination of BHT and BHA ... exerts potent anti-inflammatory activity. Our results suggest the potential usefulness of the BHT/BHA combination at an appropriate molar ratio as an antioxidant in foods and pharmaceuticals, whereas either antioxidant alone is unlikely to be effective.”

In Vivo • March 2015

Anti-inflammatory activity of the artificial antioxidants 2-tert-butyl-4-methoxyphenol (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT) and 2,4,6-tri-tert-butylphenol (TBP), and their various combinations

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Department of Diagnostic and Therapeutic Sciences

Abstract

BACKGROUND/AIM

The artificial complex phenols, 2-tert-butyl-4-methoxyphenol (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT) and 2,4,6-tri-tert-butylphenol (TBP) exert efficient antioxidant activity; however, they are considerable toxic and potentially tumor-promoting. These phenols, particularly in combinations, have enhanced antioxidant activity due to synergistic interactions and produce bioactive intermediates such as quinone methide. We investigated the anti-inflammatory activity of BHA, BHT and TBP, and combinations of BHT/BHA (in molar ratios of 1:1, 1:2, 1:3 and 2:1), BHT/TBP (1:1), and BHA/TBP (1:1), using gene-expression systems for cyclooxygenase-2 (Cox2) and tumor necrosis facto-alpha (Tnfa) in RAW264.7 cells.

MATERIALS AND METHODS

The inhibitory effects of BHA, BHT and TBP on expression of Cox2 and Tnfa genes upon stimulation with Escherichia coli lipopolysaccharide (LPS) or Porphyomonas gingivalis (Pg) fimbriae were determined using real-time polymerase chain reaction.

RESULTS

The inhibitory effect on expression of Cox2 and Tnfa genes upon stimulation with LPS and fimbriae was greatly enhanced by the combination of two antioxidants (molar ratio 1:1), BHT/BHA. In addition, that of the Cox2 gene, but not of Tnfa gene was slightly enhanced by a combination of equimolar BHT/TBP and BHA/TBP. None of the antioxidants alone exerted any anti-inflammatory activity upon stimulation with LPS, but a slight anti-inflammatory activity was observed upon stimulation with Pg fimbriae. The inhibitory effect of the BHT/BHA combination on expression of Cox2 mRNA upon stimulation with LPS was investigated at afferent molar ratios, and a molar ratio of 1:1 was found to have considerably less effect than a molar ratio of 1:2 or 2:1. The 1:3 combination had no effect.

CONCLUSION

The combination of BHT and BHA at a molar ratio of 0.5-2 exerts potent anti-inflammatory activity. This anti-inflammatory activity on the generation of inflammatory mediators in LPS-activated RAW264.7 cells may be attributable to complex synergistic antioxidant activity of the combination of BHT and BHA. Our results suggest the potential usefulness of the BHT/BHA combination at an appropriate molar ratio as an antioxidant in foods and pharmaceuticals, whereas either antioxidant alone is unlikely to be effective.

http://www.ncbi.nlm.nih.gov/pubmed/25792646

“Satisfactory results revealed that this work offered a new way for the sensitive and simple determination of BHA in complex samples.”

Talanta • June 2015

High-selective and sensitive voltammetric sensor for butylated hydroxyanisole based on AuNPs-PVP-graphene nanocomposites

Author information

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Abstract

Gold nanoparticles (AuNPs) and reduced graphene oxide (graphene) composites were synthesized via a simple one-pot approach in the presence of polyvinylpyrrolidone (PVP). Further, the Au-PVP-graphene nanocomposite was used as a new sensing material for the electrochemical detection of butylated hydroxyanisole (BHA). Because of the greatly enlarged surface area, the enhanced electron transfer rate, and a stronger enrichment of BHA, the sensor based on Au-PVP-graphene modified glassy carbon electrode (GCE) displayed highly sensitive electrochemical responses to BHA. Applying linear sweep voltammetry, a good linear relationship of the oxidation peak current with respect to concentrations of BHA across the range of 0.2-100.0 μM and a detection limit of 0.04 μM was achieved. The practical analytical performance of the Au-PVP-graphene/GCE was examined by evaluating detection of BHA in soybean oil and the flour samples. Satisfactory results revealed that this work offered a new way for the sensitive and simple determination of BHA in complex samples.

http://www.ncbi.nlm.nih.gov/pubmed/25863387

“The results show the strong hepatoprotective activity of BHA which could be due to its potent antioxidant effects.”

Toxicology And Industrial Health • November 2015

Ameliorative effect of butylated hydroxyanisole against ferric nitrilotriacetate-induced hepatotoxicity and oxidative stress in rats

Author information

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Abstract

Ferric nitrilotriacetate (Fe-NTA) is a known renal carcinogen and has been shown to adversely induce oxidative stress and tissue toxicity after both acute and chronic exposure. Present studies were designed to study the hepatoprotective and antioxidant potential of butylated hydroxyanisole (BHA), a phenolic antioxidant used in foods on ferric nitrilotriacetate (Fe-NTA) induced hepatotoxicity in rats. Male albino rats of Wistar strain (4-6 weeks old) weighing 125-150 g were used in this study. Animals were given a single dose of Fe-NTA (9 mg/kg body weight, intraperitoneal) after a week’s treatment with BHA. BHA was administered orally once daily for 7 days at doses of 1 and 2 mg/animal/day. The hepatoprotective activity was assessed using various biochemical parameters as serum transaminases (alanine transaminase (ALT), aspartate transaminase (AST)) and lactate dehydrogenase (LDH). Fe-NTA treatment increased ALT, AST, and LDH levels significantly when compared to the corresponding saline-treated group ($p < 0.001$). Fe-NTA also depleted the levels of glutathione and the activities of antioxidant enzymes namely glutathione reductase and glutathione-S-tranferase ($p < 0.05$). Pretreatment with BHA significantly decreased ALT, AST and LDH levels in a dose-dependent manner ($p < 0.05$). BHA also increased antioxidant enzymes level and decreased lipid peroxidation and hydrogen peroxide generation to 1.3-1.5-fold as compared to Fe-NTA-treated group. The results show the strong hepatoprotective activity of BHA which could be due to its potent antioxidant effects.

http://www.ncbi.nlm.nih.gov/pubmed/26499990

Food Chemistry • December 2015

Binding properties and structure-affinity relationships of food antioxidant butylated hydroxyanisole and its metabolites with lysozyme

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Abstract

“**Considering the harmful impact of food antioxidants on human bodies, thoroughly exposing their potential effects at the molecular level is important. In this study, the binding interactions of butylated hydroxyanisole (BHA), a phenolic antioxidant, and its different major metabolites** tert-butylhydroquinone (TBHQ) and tert-butylbenzoquinone (TBQ) with lysozyme were examined via fluorescence, three-dimensional fluorescence, circular dichroism (CD), and ligand-protein docking studies. The three compounds caused strong quenching of lysozyme fluorescence by a static quenching mechanism but with different quenching efficiencies and different effects on the ß-helix content of the lysozyme. The order of binding affinity of lysozyme for all test compounds is as follows: BHA>TBQ>TBHQ. Thermodynamic parameters indicated that hydrogen bonding and van der Waals forces perform dominant functions in the binding between these compounds and lysozyme. Furthermore, structure-affinity relationships between the model compounds and lysozyme were established on the basis of computational analyses.”

http://www.ncbi.nlm.nih.gov/pubmed/26041206

“Effect of thyme Essential Oil was significant (P < 0.05) and remarkable, not allowing any coliform bacteria to grow in the samples. Given that Essential Oils were obtained from natural sources, the data suggested that the **Essential Oils might be more useful than their synthetic counterparts, BHA and BHT,** as additives for chicken patties to maintain oxidative/microbial stability and increase shelf life.”

Poultry Science • February 2014

Effect of thyme/cumin essential oils and butylated hydroxyl anisole/butylated hydroxyl toluene on physicochemical properties and oxidative/microbial stability of chicken patties

Author information

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Abstract

In this study, effects of thyme/cumin essential oils (EO) and butylated hydroxyl anisole (BHA)/butylated hydroxyl toluene (BHT) on physicochemical properties and storage stability of chicken patties were compared in different storage periods (0, 3, 7, 14, 21, and 28 d). It was found that there were significant (P < 0.05) differences between physicochemical properties of patty samples treated with EO and the synthetic antioxidants. The EO showed similar performance to those of BHA and BHT in limiting TBARS values of chicken patty samples. Similarity in performance was also the case for microbial stability (total aerobic mesophilic, psychrotrophic, lactic acid, and coliform bacteria as well as molds and yeasts); namely, their effects were significant (P < 0.05). Effect of thyme EO was significant (P < 0.05) and remarkable, not allowing any coliform bacteria to grow in the samples. Given that EO were obtained from natural sources, the data suggested that the EO might be more useful than their synthetic counterparts, BHA and BHT, as additives for chicken patties to maintain oxidative/microbial stability and increase shelf life.

http://www.ncbi.nlm.nih.gov/pubmed/24570469

“We demonstrated that binary mixtures of both chemicals induce greater cytotoxic effects than those reported after single exposure to each compound. Simultaneous treatment with butylated hydroxyanisole and propylparaben caused G0/G1 cell cycle arrest as a result of enhanced generation of oxidative stress and DNA double strand breaks.”

Food And Chemical Toxicology • October 2014

The antioxidant butylated hydroxyanisole potentiates the toxic effects of propylparaben in cultured mammalian cells

Author information

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Abstract

Butylated hydroxyanisole and propylparaben are phenolic preservatives commonly used in food, pharmaceutical and personal care products. Both chemicals have been subjected to extensive toxicological studies, due to the growing concern regarding their possible impacts on environmental and human health. However, the cytotoxicity and underlying mechanisms of co-exposure to these compounds have not been explored. In this study, a set of relevant cytotoxicity endpoints including cell viability and proliferation, oxidative stress, DNA damage and gene expression changes were analyzed to assess whether the antioxidant butylated hydroxyanisole could prevent the pro-oxidant effects caused by propylparaben in Vero cells. We demonstrated that binary mixtures of both chemicals induce greater cytotoxic effects than those reported after single exposure to each compound. Simultaneous treatment with butylated hydroxyanisole and propylparaben caused G0/G1 cell cycle arrest as a result of enhanced generation of oxidative stress and DNA double strand breaks. DNA microarray analysis revealed that a cross-talk between transforming growth factor beta (TGFß) and ataxia-telangiectasia mutated kinase (ATM) pathways regulates the response of Vero cells to the tested compounds in binary mixture. Our findings indicate that butylated hydroxyanisole potentiates the pro-oxidant effects of propylparaben in cultured mammalian cells and provide useful information for their safety assessment.

http://www.ncbi.nlm.nih.gov/pubmed/25086368

Journal Of Photochemistry And Photobioliogy, Part B • December 2014

Intercalation binding of food antioxidant butylated hydroxyanisole to calf thymus DNA

Author information

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Abstract

The binding properties of food antioxidant butylated hydroxyanisole (BHA) associated with calf thymus DNA (ctDNA) in physiological buffer (pH 7.4) were investigated. Experimental results based on fluorescence, UV-vis absorption, circular dichroism (CD), viscosity measurements and autodocking techniques confirmed the intercalation binding between BHA and ctDNA. The changes in Fourier transform infrared spectra of ctDNA induced by BHA suggested that BHA was more prone to bind to G-C rich region of ctDNA, which was further ascertained with the molecular docking studies. Analysis of the CD spectra indicated that this binding interaction led to a transformation from B-like DNA structure toward A-like conformation. The complexation of BHA with ctDNA was driven mainly by hydrogen bonds and hydrophobic forces. The binding constants of the BHA-ctDNA complex were calculated to be 2.03 × 10(4), 1.92 × 10(4) and 1.59 × 10(4)L mol(-1) at 298, 304 and 310 K, respectively. Gel electrophoresis results suggested that intercalated BHA molecules did not significantly affect plasmid DNA. Moreover, the concentration profiles and the spectra for the three reaction components (BHA, ctDNA, and BHA-ctDNA complex) of the system by resolving the augmented UV-vis spectral data matrix with the use of multivariate curve resolution-alternating least squares approach provided quantitative data to estimate the progress of BHA-ctDNA interaction. This study is expected to provide new insights into the mechanism of interaction between BHA and ctDNA.

http://www.ncbi.nlm.nih.gov/pubmed/25463675

Clujul Medical • February 2013

Endocrine disrupting effects of butylated hydroxyanisole (BHA - E320)

Author information

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Abstract

“Butylated hydroxyanisole (BHA) is extensively used as antioxidant in foods, food packaging, cosmetics and pharmaceuticals. In the past years, it raised concerns regarding its possible endocrine disrupting effect. The existing in vitro studies indicate that BHA presents a weak estrogenic effect and also anti-androgenic properties while an in vivo study found it to have antiestrogenic properties. **There is no sufficient data available at the moment to draw a conclusion regarding the safety of BHA when referring to its endocrine disrupting effect. Since a fraction of the population might be exposed to doses superior to the acceptable daily intake (ADI), it is important to gather more in vitro and in vivo data concerning the potential effects that BHA might have alone, but also in mixtures with natural hormones or other endocrine disrupting compounds.**”

http://www.ncbi.nlm.nih.gov/pubmed/26527908

“In addition, single-strand DNA breakage has been observed through the comet assay technique. In addition, the morphology of DAPI-stained cells and DNA fragmentation assay using gel electrophoresis showed clear fragmentation in the chromatin and DNA rings within the nucleus of cells treated with BHA.”

DNA Cell Biology • March 2013

Cytotoxicity and DNA fragmentation properties of butylated hydroxyanisole

Author information

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Abstract

Butylated hydroxyanisole (BHA) is a synthetic phenolic food additive that is used to prevent oils, fats, and shortenings from oxidative deterioration and rancidity. It was tested for potential cytotoxicity and genotoxicity upon A549 lung cancer cells. MTT assay and flow cytometry analysis were used for cytotoxicity assessment, whereas genotoxicity was evaluated in vitro by DAPI staining, alkaline comet, and DNA fragmentation assays. BHA dose- and time-dependently decreased the growth of A549 cells with an IC50 of <0.55, 0.4, and 0.3 mM BHA at 24, 48, and 72 h, respectively. Primary and late apoptosis in the treated cells was determined using the flow cytometry analyses. In addition, single-strand DNA breakage has been observed through the comet assay technique. In addition, the morphology of DAPI-stained cells and DNA fragmentation assay using gel electrophoresis showed clear fragmentation in the chromatin and DNA rings within the nucleus of cells treated with BHA.

http://www.ncbi.nlm.nih.gov/pubmed/23413972

“Our study clearly demonstrated that inhibiting the occurrence of TAMs by BHA contributes to the inhibition of tobacco smoke carcinogen-induced tumorigenesis, suggesting ROS inhibitors may serve as a therapeutic target for treating smoke-induced lung cancer.”

Cancers (Basel) • December 2013

Butylated hydroxyanisole blocks the occurrence of tumor associated macrophages in tobacco smoke carcinogen-induced lung tumorigenesis

Author information

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Abstract

Tumor-associated macrophages (TAMs) promote tumorigenesis because of their proangiogenic and immune-suppressive functions. Here, we report that butylated hydroxyanisole (BHA) blocks occurrence of tumor associated macrophages (TAMs) in tobacco smoke carcinogen-induced lung tumorigenesis. Continuous administration of butylated hydroxyanisole (BHA), a ROS inhibitor, before or after NNK treatment significantly blocked tumor development, although less effectively when BHA is administered after NNK treatment. Strikingly, BHA abolished the occurrence of F4/80+ macrophages with similar efficiency no matter whether it was administered before or after NNK treatment. Detection of cells from bronchioalveolar lavage fluid (BALF) confirmed that BHA markedly inhibited the accumulation of macrophages while slightly reducing the number of lymphocytes that were induced by NNK. Immunohistological staining showed that BHA specifically abolished the occurrence of CD206+ TAMs when it was administered before or after NNK treatment. Western blot analysis of TAMs markers, arginase I and Ym-1, showed that BHA blocked NNK-induced TAMs accumulation. Our study clearly demonstrated that inhibiting the occurrence of TAMs by BHA contributes to the inhibition of tobacco smoke carcinogen-induced tumorigenesis, suggesting ROS inhibitors may serve as a therapeutic target for treating smoke-induced lung cancer.

Full text, graphs, charts and 20 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3875958/

“Based on these observations it can be concluded that BHA promotes immune responses by increasing T cells and activating phagocytosis by macrophages in normal mice.”

Molecular Medicine Reports • March 2012

Butylated hydroxyanisole affects immunomodulation and promotes macrophage phagocytosis in normal BALB/c mice

Author information

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Abstract

Butylated hydroxyanisole (BHA), a synthetic antioxidant, has been used in fat and fatty foods to prevent oxidative deterioration. However, the functions of BHA on immune responses in normal mice remain elusive. The aim of the present study was to investigate the effects of oral treatment of BHA on immune responses in normal mice in vivo. BALB/c mice received various treatments. Blood samples were collected and analyzed. Flow cytometry was used to determine the levels of the cell markers. Results showed that BHA did not significantly affect the weight of the animal body and spleen in normal mice. BHA promoted macrophage phagocytosis from peripheral blood mononuclear cells, but did not alter this process in the peritoneal cavity. Furthermore, BHA did not influence natural-killer cell cytotoxicity in normal mice. Notably, BHA promoted the levels of CD3 (T cells) and decreased the level of CD19 (B cells), but did not significantly affect the levels of CD11b (monocytes) and macrophages (Mac-3) in normal mice. Based on these observations it can be concluded that BHA promotes immune responses by increasing T cells and activating phagocytosis by macrophages in normal mice. However, the molecular mechanisms require further investigation.

http://www.ncbi.nlm.nih.gov/pubmed/22159551

Pharmacognosy Reviews • July 2010

Free radicals, antioxidants and functional foods: Impact on human health

Author information

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Abstract

“In recent years, there has been a great deal of attention toward the field of free radical chemistry. Free radicals reactive oxygen species and reactive nitrogen species are generated by our body by various endogenous systems, exposure to different physiochemical conditions or pathological states. A balance between free radicals and antioxidants is necessary for proper physiological function. If free radicals overwhelm the body’s ability to regulate them, a condition known as oxidative stress ensues. Free radicals thus adversely alter lipids, proteins, and DNA and trigger a number of human diseases. Hence application of external source of antioxidants can assist in coping this oxidative stress. **Synthetic antioxidants such as butylated hydroxytoluene and butylated hydroxyanisole have recently been reported to be dangerous for human health.** Thus, the search for effective, nontoxic natural compounds with antioxidative activity has been intensified in recent years. The present review provides a brief overview on oxidative stress mediated cellular damages and role of dietary antioxidants as functional foods in the management of human diseases.”

http://www.ncbi.nlm.nih.gov/pubmed/22228951

“... a 300 gram portion [10.7 ounces] of farmed Atlantic salmon would contribute up to 75% of the Acceptable Daily Intake for BHT.”

Food Additive Contamination Part A
Chemistry, Analysis, Control, Exposure And Risk Assessment • December 2010

Levels of synthetic antioxidants (ethoxyquin, butylated hydroxytoluene and butylated hydroxyanisole) in fish feed and commercially farmed fish

Author information

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Abstract

Several synthetic antioxidants are authorized for use as feed additives in the European Union. Ethoxyquin (EQ) and butylated hydroxytoluene (BHT) are generally added to fish meal and fish oil, respectively, to limit lipid oxidation. The study was conducted to examine the concentrations of EQ, BHT and butylated hydroxyanisole (BHA) in several commercially important species of farmed fish, namely Atlantic salmon, halibut and cod and rainbow trout, as well as concentrations in fish feed. The highest levels of BHT, EQ and BHA were found in farmed Atlantic salmon fillets, and were 7.60, 0.17 and 0.07 mg kg(-1), respectively. The lowest concentrations of the synthetic antioxidants found were in cod. The concentration of the oxidation product ethoxyquin dimer (EQDM) was more than ten-fold higher than the concentration of parent EQ in Atlantic salmon halibut and rainbow trout, whereas this dimer was not detected in cod fillets. The theoretical consumer exposure to the synthetic antioxidants EQ, BHA and BHT from the consumption of farmed fish was calculated. The contribution of EQ from a single portion (300 g) of skinned fillets of the different species of farmed fish would contribute at most 15% of the acceptable daily intake (ADI) for a 60 kg adult. The consumption of farmed fish would not contribute measurably to the intake of BHA; however, a 300 g portion of farmed Atlantic salmon would contribute up to 75% of the ADI for BHT.

http://www.ncbi.nlm.nih.gov/pubmed/20931417

“The acceptable daily intake (ADI) could be exceeded for sulphites and BHT by a fraction of the population, in particular within children of 9-13 years old. Among all food additive-containing foods, the highest contributors were: soft drinks to benzoates intake, nuts and canned juices to sulphites intake, bread and biscuits to BHA intake and chewing gum to BHT intake.”

Regulatory Toxicology And Pharmacology • February 2007

Dietary exposure of children and teenagers to benzoates, sulphites, butylhydroxyanisol (BHA) and butylhydroxytoluen (BHT) in Beirut (Lebanon)

Author information

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Abstract

The acceptable daily intake (ADI) for a considered chemical is by definition the amount of that substance which can be ingested every day during the life time without appreciable health risk. The theoretical risk of exceeding the ADI for benzoates, sulphites, butylhydroxyanisol (BHA) and butylhydroxytoluen (BHT) has often been examined on the basis of worst case scenario. The aim of this paper is to assess the actual intake of the food additives listed above for a group of the Lebanese population (students aged between 9 and 18 years old) likely to be highly exposed to food additives through the consumption of processed foods. Dietary exposure was obtained by combining food consumption data with food additives levels determined by chemical analysis. Food products available in Lebanon and containing added benzoates, sulphites, BHA and BHT were identified. Overall 420 samples of foods and beverages were analysed. The determination of food additives residue levels was carried out according to the official methods adopted in “Lebanese Institute for agronomic research” (IRAL) on food as consumed. The acceptable daily intake (ADI) could be exceeded for sulphites and BHT by a fraction of the population, in particular within children of 9-13 years old. Among all food additive-containing foods, the highest contributors were: soft drinks to benzoates intake, nuts and canned juices to sulphites intake, bread and biscuits to BHA intake and chewing gum to BHT intake.

http://www.ncbi.nlm.nih.gov/pubmed/16996185

“Finally, an example is shown in which gene expression profiling together with conventional biochemistry led to the discovery of novel markers **for the hepatic effects of the food additives butylated hydroxytoluene, curcumin, propyl gallate and thiabendazole.**”

Toxicology And Applied Pharmacology • September 2005

Toxicogenomics concepts and applications to study hepatic effects of food additives and chemicals

Author information

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Abstract

Transcriptomics, proteomics and metabolomics are genomics technologies with great potential in toxicological sciences. Toxicogenomics involves the integration of conventional toxicological examinations with gene, protein or metabolite expression profiles. An overview together with selected examples of the possibilities of genomics in toxicology is given. The expectations raised by toxicogenomics are earlier and more sensitive detection of toxicity. Furthermore, toxicogenomics will provide a better understanding of the mechanism of toxicity and may facilitate the prediction of toxicity of unknown compounds. Mechanism-based markers of toxicity can be discovered and improved interspecies and in vitro-in vivo extrapolations will drive model developments in toxicology. Toxicological assessment of chemical mixtures will benefit from the new molecular biological tools. In our laboratory, toxicogenomics is predominantly applied for elucidation of mechanisms of action and discovery of novel pathway-supported mechanism-based markers of liver toxicity. In addition, we aim to integrate transcriptome, proteome and metabolome data, supported by bioinformatics to develop a systems biology approach for toxicology. Transcriptomics and proteomics studies on bromobenzene-mediated hepatotoxicity in the rat are discussed. Finally, an example is shown in which gene expression profiling together with conventional biochemistry led to the discovery of novel markers for the hepatic effects of the food additives butylated hydroxytoluene, curcumin, propyl gallate and thiabendazole.

http://www.ncbi.nlm.nih.gov/pubmed/16139318

“The great cytotoxicity and apoptosis induction by BHA/BHT may be due to reactive intermediates derived from the interaction between BHA phenoxyl radical and BHT or BHT phenoxyl radical.”

Anticancer Research • November 2003

Cytotoxicity and apoptosis induction by butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)

Author information

Saito M1, Sakagami H, Fujisawa S.

Abstract

The cytotoxicity and apoptosis-inducing activity of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and 2-tert-butyl-4-methylphenol (BMP) and the mixture of BHA and BHT (BHA/BHT) (1:1, molar ratio) were investigated, using human promeylocytic leukemia cell lines (HL-60) and human squamous cell carcinoma cell lines (HSC-2). The 50% cytotoxic concentration (CC50) declined in the order of BHA, BHT (0.2-0.3 mM) > BHA/BHT (0.04-0.07 mM) > BMP (0.02-0.05 mM). The addition of antioxidants (N-acetyl-Lcysteine, sodium ascorbate, catalase) reduced the cytotoxicity of BHA/BHT or BMP against HSC-2 cells, but not that of BHA or BHT, whereas the addition of NADH, a quinone reductase to BMP, enhanced the cytotoxicity. These findings suggested that the cytotoxicity of BHA/BHT and BMP might be caused by reactive intermediates. BHA-induced cytotoxicity was enhanced by horseradish peroxidases, suggesting that BHA was oxidizable and produced cytotoxic BHA radicals. Internucleosomal DNA fragmentation of HL-60 cells was preferably induced by BHA/BHT and BMP, followed by BHA. The MnSOD mRNA expression in HL-60 cells assayed by reverse transcriptase-polymerase chain reaction was highly inhibited by BHA/BHT or BMP, accompanied by the change in the electrophoretic mobility of MnSOD on polyacryamide gel. These compounds activated caspase-3, 8 and 9 in HL-60 cells. Activations of caspases, particularly caspase-3, declined in the order of BHA/BHT > BHA > BMP > BHT. The most cytotoxic BMP activated caspase-3 activity to the least extent, possibly in part due to the occurrence of necrosis. The great cytotoxicity and apoptosis induction by BHA/BHT may be due to reactive intermediates derived from the interaction between BHA phenoxyl radical and BHT or BHT phenoxyl radical.

http://www.ncbi.nlm.nih.gov/pubmed/14981915

Food Chemistry And Toxicology • September 1999

Safety assessment of butylated hydroxyanisole and butylated hydroxytoluene as antioxidant food additives

Author information

Williams GM1, Iatropoulos MJ, Whysner J.

Department of Pathology, New York Medical College
American Health Foundation Valhalla, 10595, USA

Abstract

“Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are widely used antioxidant food additives. They have been extensively studied for potential toxicities. This review details experimental studies of genotoxicity and carcinogenicity which bear on cancer hazard assessment of exposure to humans. We conclude that BHA and BHT pose no cancer hazard and, to the contrary, may be anticarcinogenic at current levels of food additive use.”

http://www.ncbi.nlm.nih.gov/pubmed/10541460

“It is hypothesized that BHA gives rise to tumor formation in rodent forestomach by inducing heritable changes in DNA. Evidence is being provided that reactive oxygen species, in particular hydroxylradicals, may play a crucial role.”

Chemical And Biological Interactions • 1991

Butylated hydroxyanisole in perspective

Author information

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Abstract

Butylated hydroxyanisole (BHA) is a synthetic food antioxidant used to prevent oils, fats and shortenings from oxidative deterioration and rancidity. This review depicts the current knowledge on BHA. The physical and chemical characteristics of BHA are summarized and its function as a food antioxidant is made clear. The toxicological characteristics of BHA and its metabolic fate in man and animal are briefly reviewed. Special emphasis is laid on the carcinogenicity of BHA in the forestomach of rodents and to related events in the forestomach and other tissues in experimental animals. At present there is sufficient evidence for carcinogenicity of BHA, but there is hardly any indication that BHA is genotoxic. Therefore risk assessment for this epigenetic carcinogen is based on non-stochastic principles. However, the mechanism underlying the tumorigenicity of BHA is not known. In the last part of this review an attempt is made to unravel the unknown mechanism of carcinogenicity. It is hypothesized that BHA gives rise to tumor formation in rodent forestomach by inducing heritable changes in DNA. Evidence is being provided that reactive oxygen species, in particular hydroxylradicals, may play a crucial role. The key question with respect to risk assessment for BHA is whether or not the underlying mechanism is thresholded, which is important for the choice of the appropriate model to assess the risk, if any, for man and to manage any potential risk.

http://www.ncbi.nlm.nih.gov/pubmed/1934145

“Information gleaned from the BHA and EDB studies with multiple animal species facilitated regulatory decision-making regarding the potential toxicity/carcinogenicity of these compounds to man.”

Toxicology And Pathology • September 1988

Forestomach lesions induced by butylated hydroxyanisole and ethylene dibromide: a scientific and regulatory perspective

Author information

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Abstract

Selected pathology lesions from 9 studies, 5 with butylated hydroxyanisole (BHA) and 4 with ethylene dibromide (EDB) are reviewed and their relative importance in regulatory evaluation is discussed. When Fischer 344 (F344) rats were fed BHA at 0.5% and 2.0% of the diet for 2 years, an increased number of rats of both sexes had epithelial hyperplasia of the forestomach at both treatment levels, compared to controls. At the 2.0% level, an increased number of rats had forestomach papilloma or forestomach squamous cell carcinoma. In a second study, in which F344 rats were fed BHA at 1.0% and 2.0% of the diet for 2 years, increased numbers of rats in both treatment groups were reported to have hyperplasia or papilloma of the forestomach. At the 2.0% level, increased numbers of rats developed squamous cell carcinoma of the forestomach. More Syrian golden hamsters fed BHA at 1.0% and 2.0% of the diet for 2 years reportedly had hyperplasia, papilloma or squamous cell carcinoma of the forestomach than did nontreated animals. Ingestion of BHA at 0.5% and 1.0% of the diet by B6C3F1 mice for 2 years was reported to produce an increase of animals with hyperplasia or papilloma of the forestomach at both dosage levels, compared to nontreated mice. When beagle dogs were fed BHA at 1.0% and 1.3% of the diet for 180 days, no lesions/tumors of the distal esophagus or stomach were identified at gross necropsy or by light or electron microscopy. When EDB was administered by gavage to Osborne-Mendel rats and B6C3F1 mice under conditions of the National Toxicology Bioassay Program, more rats and mice, both male and female, developed squamous cell carcinoma of the forestomach than did nontreated groups. EDB administered via inhalation to F344 rats and B6C3F1 mice did not cause squamous cell carcinoma of the forestomach; however, other neoplasms occurred which were considered to be treatment-related. Information gleaned from the BHA and EDB studies with multiple animal species facilitated regulatory decision-making regarding the potential toxicity/carcinogenicity of these compounds to man.

Full text, graphs, charts and 8 references

http://tpx.sagepub.com/content/16/2/172.full.pdf

“These results suggest that the toxicity resulting from the combination of BHA and BHT is due to the formation of BHT-quinone methide and that the role of BHA might be either to deplete some protective mechanism in the target pulmonary cells or to enhance the biotransformation of BHT into BHT-quinone methide.”

Toxicology And Applied Pharmacology • October 1988

Enhancement of butylated hydroxytoluene-induced mouse lung damage by butylated hydroxyanisole

Author information

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Abstract

The phenolic antioxidant butylated hydroxytoluene (BHT) is known to produce a dose-dependent increase in mouse lung weight which is characterized by the necrosis of pulmonary type I and endothelial cells. We studied the ability of butylated hydroxyanisole (BHA) to modify BHT-induced changes in lung weight in male CD-1 mice. BHA alone had no effect on lung weight up to a dose of 500 mg/kg (sc). However, when injected 30 minutes prior to sub-threshold doses of BHT (0-250 mg/kg, ip), BHA significantly enhanced lung weight in a dose-dependent manner. The ability of BHA to enhance BHT-induced changes in lung weight was dependent on both the time and the route of administration of BHA relative to BHT. Deuteration of BHT abolished the in vivo toxicity from the combination of BHA and BHT. These results suggest that the toxicity resulting from the combination of BHA and BHT is due to the formation of BHT-quinone methide and that the role of BHA might be either to deplete some protective mechanism in the target pulmonary cells or to enhance the biotransformation of BHT into BHT-quinone methide.

http://www.ncbi.nlm.nih.gov/pubmed/3188016

“BHA clearly induced squamous cell carcinomas in both the rat and hamster forestomach. BHT demonstrated promotion potential for urinary bladder and MNU-initiated thyroid carcinogenesis ...”

Toxicology And Pathology • August 1986

Modifying effects of antioxidants on chemical carcinogenesis

Ito N, Hirose M, Fukushima S, Tsuda H, Tatematsu M, Asamoto M.

Abstract

Studies were made on the carcinogenic activity of butylated hydroxyanisole (BHA) in rats, mice, and hamsters and the effect of the antioxidants BHA, butylated hydroxytoluene (BHT), ethoxyquin (EQ), sodium L-ascorbate (SA), ascorbic acid (AA), sodium erythorbate (SE), propyl gallate (PG), and alpha-tocopherol, on two-stage chemical carcinogenesis in rats initiated with N-methyl-N’-nitro-N-nitrosoguanidine (MNNG), 1,2-dimethylhydrazine (DMH), diethylnitrosamine (DEN), 7,12-dimethylbenz(a)anthracene (DMBA), N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), N-ethyl-N-hydroxyethylnitrosamine (EHEN), or N-methylnitrosourea (MNU). BHA clearly induced squamous cell carcinomas in both the rat and hamster forestomach. The tumorigenic action of crude BHA on the forestomach is largely due to 3-tert-BHA. In two-stage chemical carcinogenesis, BHA promoted MNNG or MNU-initiated forestomach and BBN- or MNU-initiated urinary bladder carcinogenesis and inhibited DEN- or EHEN-initiated liver and DMBA-initiated mammary carcinogenesis. BHT demonstrated promotion potential for urinary bladder and MNU-initiated thyroid carcinogenesis and inhibited DMBA-initiated ear duct carcinogenesis. EQ promoted EHEN-initiated kidney carcinogenesis and inhibited DMBA-initiated mammary and EHEN-initiated liver carcinogenesis. SA promoted forestomach and urinary bladder carcinogenesis and SE likewise enhanced urinary bladder carcinogenesis. alpha-Tocopherol inhibited ear duct carcinogenesis. No effects of any of the antioxidants on glandular stomach carcinogenesis were found. The results clearly demonstrated that antioxidants have different effects (promoting or inhibitory influences) depending on the organ studied and suggest the importance of a whole body approach to their investigation.

Full text, PDF, graphs, charts and 38 references

http://tpx.sagepub.com/content/14/3/315.full.pdf

“The BHT was fed to Wistar rats at 0, 25, 100 and 250 mg/kg body weight. At the highest dose there was an increase in the number of rats with hepatocellular adenoma and with hepatocellular carcinoma.”

Food Chemistry Toxicology • October 1986

Pathology of BHA- and BHT-induced lesions

By R.W. Moch

Abstract

The pathology lesions from three studies, two with butylated hydroxyanisole (BHA) and one with butylated hydroxytoluene (BHT), are reviewed. When BHA was fed at 0.5 and 2.0% of the diet to F344 rats for two years, there was an increase in epithelial hyperplasia of the forestomach at both treatment levels. Papilloma and squamous-cell carcinoma of the forestomach were increased at the 2.0% level. When BHA was fed to beagle dogs at 1.0 and 1.3% of the diet for 180 days, no lesions/tumours of the distal oesophagus or stomach could be identified either at gross necropsy or by light or electron microscopy. The BHT was fed to Wistar rats at 0, 25, 100 and 250 mg/kg body weight. At the highest dose there was an increase in the number of rats with hepatocellular adenoma and with hepatocellular carcinoma.

http://www.ncbi.nlm.nih.gov/pubmed/3804118

“This clearly indicates that at the concentrations of 0.75%, BHA and BHT are harmful to the blood. Thus while BHA and BHT are known to be metabolized in the liver and eliminated through the urine, they might be very detrimental to the circulatory system.”

Environmental Research • October 1986

Effect of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) on rat erythrocytes

Jayalakshmi CP, Sharma JD.

Abstract

The widespread use of antioxidants in the food processing industries, especially oil and oil based ones, has great economic advantages. Yet since the ban on the further usage of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) by the FAO in 1980, there have been several reports indicating that BHA and BHT might have both beneficial and detrimental effects. Studies were performed in healthy mature rats both males and females in a 1:1 ratio. In vitro estimations of the percentage hemolysis (50% hemolysis indicating a 50% toxicity level) showed that BHT is more toxic than BHA and the hemolytic activities (kinetics) showed a peak at 60-65% after 12 min with BHT and at 50% after 20 min with BHA. This clearly indicates that at the concentrations of 0.75%, BHA and BHT are harmful to the blood. Further work of dietary effects on blood is in progress. Thus while BHA and BHT are known to be metabolized in the liver and eliminated through the urine, they might be very detrimental to the circulatory system.

http://www.ncbi.nlm.nih.gov/pubmed/3757972

Critical Reviews In Toxicology • July 1985

Carcinogenicity and modification of the carcinogenic response by BHA, BHT, and other antioxidants

Ito N, Fukushima S, Tsuda H.

Abstract

"Carcinogenicity tests showed that addition of the antioxidant BHA to the diet of F344 rats induced high incidences of papilloma and squamous cell carcinoma of the forestomach of both sexes. Male hamsters given BHA for 24 weeks also developed papilloma showing downward growth into the submucosa of the forestomach. These results indicate that BHA should be classified in the category of "sufficient evidence of carcinogenicity" as judged by IARC criteria. The 3-tert isomer of BHA seemed to be responsible for the carcinogenicity of crude BHA in the forestomach of rats. BHT was not found to be carcinogenic in rats or mice. In two-stage carcinogenesis in rats after appropriate initiation, BHA enhanced carcinogenesis in the forestomach and urinary bladder of rats, but inhibited carcinogenesis in the liver. BHT enhanced the induction of urinary bladder tumors and inhibited that of liver tumors, but had no effect on carcinogenesis in the forestomach. BHT could be a promoter of thyroid carcinogenesis. Sodium L-ascorbate enhanced forestomach and urinary bladder carcinogenesis. Ethoxyquin enhanced kidney and urinary bladder carcinogenesis, but inhibited liver carcinogenesis. Thus, these antioxidants modify two-stage chemical carcinogenesis in the forestomach, liver, kidney, urinary bladder, and thyroid, but show organ-specific differences in effects."

http://www.ncbi.nlm.nih.gov/pubmed/3899519

“It is emphasized that the approval of chemicals for use in the food industry through toxicity studies **does not necessarily guarantee against the hazards of toxicity**, especially during infancy.”

Clinical Toxicology • October 1979

Infantile methemoglobinemia caused by food additives

Nitzan M, Volovitz B, Topper E.

Abstract

A small outbreak of toxic methemoglobinemia occurred among infants in a pediatric ward. Investigation revealed that the most likely source of toxicity was an approved fat preservative which had been added to a soybean infant formula by the manufacturer. This fat preservative contained three phenolic compounds having highly effective antioxygenic properties (butylated hydroxyanisole, butylated hydroxytoluene and propyl gallate). The outbreak ceased when the offending agents were eliminated from the food preparation. It is emphasized that the approval of chemicals for use in the food industry through toxicity studies does not necessarily guarantee against the hazards of toxicity, especially during infancy.

http://www.ncbi.nlm.nih.gov/pubmed/509890

CHAPTER SEVENTEEN

Synergy

The Peer Review

Websters Dictionary defines the word synergy as:

1. the interaction of elements that when combined produce a total effect that is greater than the sum of the individual elements, contributions, etc.; synergism.
2. Physiology, Medicine/Medical. the cooperative action of two or more muscles, nerves, or the like.
3. Biochemistry, Pharmacology. the cooperative action of two or more stimuli or drugs.

Synergy of various kinds has been advanced by Peter Corning as a causal agency that can explain the progressive evolution of complexity in living systems over the course of time. According to the Synergism Hypothesis, synergistic effects have been the drivers of cooperative relationships of all kinds and at all levels in living systems. The thesis, in a nutshell, is that synergistic effects have often provided functional advantages (economic benefits) in relation to survival and reproduction that have been favored by natural selection. The cooperating parts, elements, or individuals become, in effect, functional "units" of selection in evolutionary change. Similarly, environmental systems may react in a non-linear way to perturbations, such as climate change, so that the outcome may be greater than the sum of the individual component alterations. Synergistic responses are a complicating factor in environmental modeling.

Pest synergy would occur in a biological host organism population, where, for example, the introduction of parasite A may cause 10% fatalities, and parasite B may also cause 10% loss. When both parasites are present, the losses would normally be expected to total less than 20%, yet, in some cases, losses are significantly greater. In such cases, it is said that the parasites in combination have a synergistic effect.

Drug synergy occurs when drugs can interact in ways that enhance or magnify one or more effects, or side-effects, of those drugs. This is sometimes exploited in combination preparations, such as codeine mixed with acetaminophen or ibuprofen to enhance the action of codeine as a pain reliever. Some drug users frequently utilize 5-HTP, a serotonin precursor often used as an antidepressant, prior to and after ingestion of MDMA. It is said to increase the "high" and decreases the "comedown" stages of MDMA use, although most anecdotal evidence has pointed to 5-HTP significantly altering the effect of MDMA when used at the same time, as well as potentiating the side effects associated with serotonin syndrome. Other examples include the use of cannabis with LSD, where the active chemicals in cannabis have been reported to enhance the hallucinatory experience of LSD.

Negative effects of synergy are a form of contraindication. For example, a combination of depressant drugs that affect the central nervous system (CNS), such as alcohol and Valium, can cause a greater reaction than simply the sum of the individual effects of each drug if they were used separately. In this particular case, the most serious consequence of drug synergy is exaggerated respiratory depression, which can be fatal if left untreated. Mixing drugs can produce potentially fatal reactions within the brain, such as serotonin syndrome, due to synergistic reactions changing chemical and receptor activity. In the case of Monoamine oxidase inhibitor (MAOI) medications, mainly used as last-straw antidepressants, mixing

certain foods and drugs may cause hypertension or hyperserotonemia.

Drug synergy can occur both in biological activity and because of pharmacokinetics. Shared metabolic enzymes can cause drugs to remain in the bloodstream much longer in higher concentrations than if individually taken.

A paper presenting a community computational challenge to predict synergy outlines the difficulty of predicting synergy based on high-throughput data. The Food and Drug Administration published a guideline for the pharmaceutical industry stressing the need to understand combination effects and synergy.

The following are further sample mechanisms that may be involved in the development of synergistic effects:

• improvement of absorption or bioavailability (bioenhancer; for example loperamide reduces the motility of the small intestine, thus increasing the absorption of many drugs absorbed in the small intestine).
• displacement of an agent from plasma proteins to which it usually binds, whereby the non-bound and thus the effective fraction of the agent is increased.
• Binding to similar receptors (e.g. two ACE inhibitors may bind to the same receptor).
• Effect on the same cellular system (e.g. two different antibiotics like a penicillin and an aminoglycoside; penicillins damage the cell wall of gram-positive bacteria and improve the penetration of aminoglycosides).
• Prevention or delay of degradation in the body (e.g. the antibiotic Ciprofloxacin inhibits the metabolism of Theophyllin).
• Slowdown of excretion (e.g. Probenecid delays the [nephron|tubular] secretion of Penicillin in the kidney and thus prolongs its effect).
• Anticounteractive action, for example the effect of oxaliplatin and irinotecan. Oxaliplatin intercalates DNA whereby the cell is not able to replicate DNA. Then, topoisomerase 1 tries to repair the damage. Irinotecan inhibits topoisomerase 1, consequently the cytostatic effect is increased.

Toxicological synergy is of concern to the public and regulatory agencies because chemicals individually considered safe might pose unacceptable health or ecological risk in combination. Articles in scientific and lay journals include many definitions of chemical or toxicological synergy, often vague or in conflict with each other. Because toxic interactions are defined relative to the expectation under "no interaction", a determination of synergy (or antagonism) depends on what is meant by "no interaction". The United States Environmental Protection Agency has one of the more detailed and precise definitions of toxic interaction, designed to facilitate risk assessment. In their guidance documents, the no-interaction default assumption is dose addition, so synergy means a mixture response that exceeds that predicted from dose addition. The EPA emphasizes that synergy does not always make a mixture dangerous, nor does antagonism always make the mixture safe; each depends on the predicted risk under dose addition.

For example, a consequence of pesticide use is the risk of health effects. During the registration of pesticides in the United States exhaustive tests are performed to discern health effects on humans at various exposure levels. A regulatory upper limit of presence in foods is then placed on this pesticide. As long as residues in the food stay below this regulatory level, health effects are deemed highly unlikely and the food is considered safe to consume.

However, in normal agricultural practice, it is rare to use only a single pesticide. During the production of a crop, several different materials may be used. Each of them has had determined a regulatory level at which they would be considered individually safe. In many cases, a commercial pesticide is itself a combination of several chemical agents, and thus the safe levels actually represent levels of the mixture. In contrast, a combination created by the end user, such as a farmer, has rarely been tested in that combination. The potential for synergy is then unknown or estimated from data on similar combinations. This lack of information also applies to many of the chemical combinations to which humans are exposed, including residues in food, indoor air contaminants, and occupational exposures to chemicals. Some groups think that the rising rates of cancer, asthma, and other health problems may be caused by these combination exposures; others have alternative explanations. This question will likely be answered only after years of exposure by the population and decades of synergistic research on chemical toxicity, and even then we may not decipher the mechanisms behind these complex mixtures.

Frontiers In Public Health • January 2016

Food-Based Interventions to Modify Diet Quality and Diversity to Address Multiple Micronutrient Deficiency

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FOOD SYNERGY

Excerpts

INTRODUCTION

Globally, an estimated two billion people suffer from a chronic deficiency of micronutrients (1). In developing countries, multiple micronutrient deficiencies often occur concurrently in the same population [1]. Even mild to moderate deficiencies of micronutrients lead to impaired physical and cognitive development, poor physical growth, and work capacity and thereby considered as hidden hunger, which impact the nation's development (6). Three-pronged strategy has been envisaged for prevention and control of hidden hunger, which can be deployed individually or in combination: short-term supplementation, medium-term food fortification, and a long-term focus on dietary diversification. Success in the past with respect to supplementation or fortification strategies could be attributed to reduction of specific clinical forms of micronutrient deficiency prevalent in the population such as Pellagra (niacin), beri-beri (vitamin B1), rickets (vitamin D), goiter (iodine), and neural tube defects (folic acid). The clinical prevalence of Bitot's spot (vitamin A deficiency) has come down and nutritional blindness has been eliminated. However, the presence of subclinical forms of deficiency is more than 40% (7). The same situation can be attributed to anemia due to iron deficiency with severe forms of anemia reduced to <2% with mild moderate anemia now accounting to more than 50% (2). Inadequacies of vitamin D, vitamin B-12, and zinc based on biomarkers have been reported.

Dietary Diversity and Functional Outcomes - Growth

Systematic review has shown that in economically disadvantaged countries, diet quality indices may be predictive of child growth (47). Data from 11 recent Demographic and Health Surveys (DHS) have been used to examine the association between dietary diversity and height-for-age Z-scores (HAZ) for 6–23 month-old children, while controlling for household wealth/welfare and several other potentially confounding factors. Dietary diversity was significantly associated with HAZ, either as a main effect or in an interaction in ten out of eleven countries (48). Evidence links dietary diversity with child stunting among 11-, 12–23-, and 24–59-month-old children of rural Bangladesh (49) and in a nationally representative sample of 6209 children aged 12–59 months in Cambodia (50). Dietary diversity has been associated with anthropometry in 6–23 month-old children of Burkina Faso also (51). Stunting has been proven to be resistant to major nutritional interventions, and therefore this association provides more light into the need for holistic approaches in targeting any nutritional issue. One prospective study looked at consumption of different foods and food groups by mother during different periods of gestation, on birth weight of the offspring. Interestingly, energy and protein intakes of mothers did not show any association with the birth size of the child but fruit, vegetable, and milk consumption did show an association (52).

Cognition

Apart from stunting, dietary quality if not diversity alone has been linked with functional outcomes such as cognition in the elderly (53–55). An association between Mediterranean diet and lesser cognitive decline has been reported by several researchers in the case of elderly (56). Cognitive performance has also been associated with dietary diversity among other children (57).

Gut Health

Diet provides nutrients not only for the host but also for the bacteria therein and therefore is one of the major determinants of gut micro biome (58). Diet per se has been unequivocally linked to gut micro biota by several studies (59–62). Fruit and vegetable intake has also been recognized as capable of altering gut micro biota (63). A linkage between dietary diversity and microbial diversity in the gut is a relatively new concept.

Using fish as the model, such an association has been elucidated, i.e., more diversity of food by the fish, less is the diversity of microorganisms in the gut which is an undesirable effect. This study done in vertebrate species if confirmed in humans suggest that multiple diet components can interact non-additively to influence gut microbial diversity and point toward intelligent food synergies for a diverse gut micro biome (64).

Dietary Diversification: From Evidence to Implementation

It is imperative to understand the challenges and opportunities for promoting dietary diversification as a sustainable strategy. Though the identified challenges and opportunities may show geographical variations, the basic framework can be applied throughout and has been presented in Box 1. The challenges may spread across, from lab to the land and from there to changing the attitude of the population by and large with progressive infiltration and a positive coalition of multiple stakeholders. This full cycle of intervention has to be a slow but rewarding process. A detailed recount of how such a concept would work in developing countries has been provided in the following sections.

Apart from the overall dimension of dietary diversity, utilizing the effects of favorable food combinations, need to be sufficiently elucidated for food-based approaches to succeed. But it need to be borne in mind that the micronutrient status per se may have an important role in regulating bioavailability which is proven at least in the case of iron (69).

Creating evidence and popularizing intelligent food synergies are required for overcoming the dueling effects of malnutrition. Food synergies are the additive or more than additive influences of foods and food constituents on health (70). Though not extensive, it is fortunate that there have been attempts both at lab and land to discern the nature of this synergy in the case of at least some of the micronutrients (71–88). However, it is a consumer-centric strategy which requires effective dissemination among the target group especially the care-givers who are often the change agents of the family with respect to nutrition.

Food Synergy for Iron Bioavailability

A typical example is iron which is an exceptional mineral and has the major homeostatic control at the site of absorption. Absorption of iron and zinc from vegetarian Indian meals is low (89, 90). Studies both in vitro and in vivo have demonstrated a synergistic effect of vitamin C, both in synthetic and food form on iron owing to its reducing property.

The molar ratios of ascorbic acid (AA) to iron for iron absorption have also been studied. Stable isotope studies have reported iron molar ratios of 2:1 or 4:1 increased iron absorption by 270 or 343%, respectively, in control subjects and by 291 or 350%, respectively, in subjects with iron deficiency anemia (91). Using radio-isotopic studies, Ballot et al. (71) have shown that papaya and guava having the maximum iron enhancing property. Stable isotope studies done in adolescents have also shown that inclusion of 100 g of guava in habitual meal had iron enhancing property at an AA molar ratio of around five (73). Therefore, fruits and minimally processed vegetables high in AA can enhance bioavailability of iron, if included in habitual meals.

Meat and oily fish are also apparently good promoters of iron absorption. However, when these two were compared in one study, meat appeared to be a better promoter than oily fish. This has been shown by a randomized cross-over trial of two 8-week periods in 25 young women. Though there were no significant differences across two groups, ferritin moderately decreased and sTfR increased with oily fish while the opposite happened in red meat group (79). Speculations have been made regarding cysteine-containing peptides being the meat factor of muscle proteins enhancing iron absorption. However, it has been demonstrated that cooking meat at 70, 95, or 120°C increased non-heme iron absorption by 0.9, 0.7, and 2% and is an argument against sulfydryl groups from cysteine residues in promoting iron absorption and the content decreases with increasing temperature (76). Lactic fermentation of vegetables is another interesting prospect, which has been reported to increase hydrated Fe^{3+} species and enhance iron absorption with low and high phytate meal (92).

Food Synergy for Provitamin A Bioavailability

Absorption of provitamin A is yet another example which has been explored with respect to fat, or other food components. This is especially important where provitamin A carotenoids contribute predominantly to vitamin A in the diet and have low efficiency of conversion (8). The amount of fat required is however inconclusive with reports of quantities as low as 2.4 g/meal possessing the promoter effect.

Apart from the presence of fat, food matrix effects such as processing may also influence the bioavailability of carotenoids. For instance, enzymatic disruption of cell wall structure enhanced bioavailability of beta-carotene from whole and minced spinach (93). Competitive inhibitory interactions have been found among the different carotenoids from various vegetable sources but did not diminish plasma carotenoid concentration (94). Surprisingly, consumption of daily recommended vegetables in one meal rather than smaller doses over multiple meals with oil exhibited the greatest absorption of carotenoids (95). Amount and source of lipid may also affect carotenoid bioavailability. Mono unsaturated fatty acids rich canola oil trended toward a higher alpha carotene and lutein absorption compared to saturated fatty acid rich butter (96). Comparison of a saturated fat source (coconut oil rich in medium chain triglycerides) with a polyunsaturated fat source (safflower oil) on carotenoid bioaccumulation from tomato has been carried out in Mongolian Gerbril. It was observed that coconut oil enhanced tissue uptake of tomato carotenoids to a greater extent than safflower oil. Coconut oil increased serum cholesterol but decreased hepatic cholesterol compared to safflower oil (97). Apart from the examples provided, an extensive recount of the carotenoid re-absorption from plant sources in the presence or absence of dietary fat has been provided elsewhere (98). However, fat intake per se has been reported to be meager in rural populations of India (~15%) and is also a con-

cern how judiciously it can be included in even in the diets of urban population (99).

Food Synergy and Zinc Bioavailability

In the case of zinc, the protein quality and quantity, phytate and fiber, calcium, iron, cadmium, copper, and several low molecular weight ligands have been implicated and reviewed elsewhere (100). However, with the available evidence including even a small amount of animal protein from fish, poultry, guinea fowl, rabbit, goat, or eggs increases zinc (as well as non-heme iron) absorption. This enhancing effect has been linked with certain amino acid and cysteine-containing peptides released during the digestion of animal protein, forming soluble ligands with zinc. Phytate reducing properties such as soaking, germination and fermentation can also be utilized for improving zinc bioavailability at household level (101).

Vitamin D, Calcium, and Physical Activity

Tropical countries have an advantage of ample sunshine which needs to be harnessed for attaining vitamin D sufficiency and calcium balance. While life style modification with more emphasis on outdoor physical activity may prove to be beneficial for one segment of population, more evidence need to be brought out regarding strategies to be adopted in situations where sun exposure does not seem to be the sole reason. Built environment conducive for safe sun exposure may also prove to be beneficial (102).

Food Antagonisms and the Role of Food Processing

The existence of food antagonisms have been demonstrated in the presence of phytates, tannins, and oxalates with respect to iron, zinc, and calcium (103). Appropriate processing of food can bring about significant improvement in micronutrient bioavailability in terms of increase the physicochemical accessibility of micronutrients, decrease the content of antinutrients, such as phytate, or increase the content of compounds that improve bioavailability. The common methods include thermal processing, mechanical processing, soaking, fermentation, and germination/malting (104, 105). One systematic review has shown some benefit of cooking in iron pots on iron absorption. But knowing the limitations of iron absorption in man, it is important to understand the mechanism clearly before concluding on this strategy (106). Tea in a rice-based meal has shown inhibitory effects on iron absorption. The consumption of 1 or 2 cups of tea decreased iron absorption in the non-anemia subjects by 49 or 66%, respectively, and in the iron deficiency anemia group by 59 or 67%, respectively (91) and is yet another example for the need of intelligent food synergies. Inhibitory effect of dietary soluble fibers such as pectin, guar, alginate (mean decrease 33–43%) on beta-carotene have also been demonstrated (107).

Role of Traditional Food Systems

Exploring the traditional food systems for the protective effects offered in the past and transmitting these effects to the future need to be thought about. Though not in the case of micronutrients, the concept has been a matter of focus in the case of non-communicable diseases. The Mediterranean diet patterns originating from countries surrounding the Mediterranean Sea including France, Italy, Spain, Morocco, and Greece, a part of the world which exhibited low prevalence of non-communicable diseases exemplifies the need to explore traditional food systems. However, it needs to be borne in mind that the reproducibility of the benefits in such situation depends on a complex set of variables including geo-position, environment, ethnicity, and culture (121). The traditional food systems in India have not been researched in its full potential though methodology for documenting traditional food systems of indigenous populations have been brought out by International agencies and several indigenous populations have been studied (122). Owing to the transition which has already set in, the ways and means to research this issue need to be explored for the effective preservation of traditional food systems.

Conclusion

Promoting food-based strategies is in the nascent stages of development in developing countries. Solution-oriented transdisciplinary research with effective innovation and implementation involving multiple stakeholders and effective public–private partnership is required to tackle the problem of micronutrient insufficiency using food-based approaches. Assuming economic transition to be a solution to all problems may not be effective and therefore targeted strategies are required. Food systems that would allow healthy choice of food and facilitating the process of intelligent food synergies with home as the center point of the activity and caregiver as the change agent with effective participation from family members is required. Tracing the path that leads these changes and intervening at these critical points may result in overall health and nutrition security especially micronutrient security. Built environment changes for effective physical activity modifications and strengthening behavior change communication is required for food-based strategies to succeed.

Full text, graphs, charts and 122 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4700276/

“Oral contraceptive use and smoking acted **synergistically** to increase the risk of cervical intraepithelial neoplasia 2 or 3 in Korean women.”

Journal Of Epidemiology • January 2016

Association of Combined Tobacco Smoking and Oral Contraceptive Use With Cervical Intraepithelial Neoplasia 2 or 3 in Korean Women

Author information

Oh HY1, Kim MK, Seo SS, Lee JK.

Abstract

BACKGROUND

Cigarette smoking and oral contraceptive (OC) use have been associated with cervical neoplasia, and the combination of smoking and OC use could influence cervical carcinogenesis. We aimed to assess the joint effect of smoking and OC use on the risk of cervical intraepithelial neoplasia (CIN).

METHODS

From a cohort of human papillomavirus-positive subjects recruited from 6 hospitals in Korea from March 2006 to November 2012, a total of 678 subjects (411 control, 133 CIN 1, and 134 CIN 2 or 3 cases) were selected for this study (mean age, 43 years). The risk of CIN associated with smoking and OC use on additive and multiplicative scales was estimated via multinomial logistic regression after adjustment for potential confounding factors. The relative excess risk due to interaction (RERI) and the synergy index (S) were used to evaluate the additive interaction.

RESULTS

OC users (odds ratio [OR] 1.98; 95% confidence interval [CI], 1.07-3.69) and long-term OC use (≥20 months; OR 2.71; 95% CI, 1.11-6.59) had a higher risk of CIN 2/3, but had no association with CIN 1, compared to non-OC users. Smokers and heavy smoking (≥8 cigarettes/day) were not associated with any CIN grade. Combined smoking and OC use (OR 4.91; 95% CI, 1.68-14.4; RERI/S, 3.77/27.4; P for multiplicative interaction = 0.003) and combined heavy smoking and long-term OC use (OR 11.5; 95% CI, 1.88-70.4; RERI/S, 9.93/18.8; P for multiplicative interaction = 0.009) had a higher risk of CIN 2/3 but had no association with CIN 1 compared to combined non-smoking and non-OC use.

CONCLUSIONS

OC use and smoking acted synergistically to increase the risk of CIN 2 or 3 in Korean women.

Full text, graphs, charts and 45 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4690737/

“Our results implicate serotonin in a novel form of decision-making, demonstrate its fitness consequences, suggest that NSM serotonergic neurons and ADF serotonergic neurons act in concert to modulate locomotion in complex environments, and identify the **synergistic** action of a channel and a metabotropic receptor in accelerating C. elegans decision-making.”

BMC Biology • February 2016

Serotonin promotes exploitation in complex environments by accelerating decision-making

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Abstract

BACKGROUND

Fast responses can provide a competitive advantage when resources are inhomogeneously distributed. The nematode Caenorhabditis elegans was shown to modulate locomotion on a lawn of bacterial food in serotonin (5-HT)-dependent manners. However, potential roles for serotonergic signaling in responding to food discovery are poorly understood.

RESULTS

We found that 5-HT signaling in C. elegans facilitates efficient exploitation in complex environments by mediating a rapid response upon encountering food. Genetic or cellular manipulations leading to deficient serotonergic signaling resulted in gradual responses and defective exploitation of a patchy foraging landscape. Physiological imaging revealed that the NSM serotonergic neurons responded acutely upon encounter with newly discovered food and were key to rapid responses. In contrast, the onset of responses of ADF serotonergic neurons preceded the physical encounter with the food. The serotonin-gated chloride channel MOD-1 and the ortholog of mammalian 5-HT1 metabotropic serotonin receptors SER-4 acted in synergy to accelerate decision-making. The relevance of responding rapidly was demonstrated in patchy environments, where the absence of 5-HT signaling was detrimental to exploitation.

CONCLUSIONS

Our results implicate 5-HT in a novel form of decision-making, demonstrate its fitness consequences, suggest that NSM and ADF act in concert to modulate locomotion in complex environments, and identify the synergistic action of a channel and a metabotropic receptor in accelerating C. elegans decision-making.

Full text, graphs, charts and 75 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4743430/

“Furthermore, **synergy** was observed between olive oil and tomato carotenoids in inhibiting HT-29 cancer cell proliferation ...”

Journal Of The Science Of Food And Agriculture • April 2016

Phytochemical composition and in vitro antitumor activities of selected tomato varieties

Author information

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Abstract

BACKGROUND

Previous studies indicated that tomato is a rich source of phytochemicals that act on different tumors. In this research, the phytochemical composition of selected tomato varieties was assessed by GLC and UHPLC/HPLC-MS, as well as their antitumor activities on HT-29 colorectal cancer cells.

RESULTS

Significant differences were found among tomato varieties; lycopene was high in Racimo; phenolics in Pera; sterols in Cherry; and linoleic acid predominated in all varieties. The MTT and LDH assays showed significant time- and concentration-dependent inhibitory/cytotoxic effects of all tomato varieties on HT-29 cells. Furthermore, the joint addition of tomato carotenoids and olive oil to HT-29 cell cultures induced inhibitory effects significantly higher than those obtained from each of them acting separately, while no actions were exercised in CCD-18 normal cells.

CONCLUSION

Tomato fruits constitute a healthy source of phytochemicals, although differences exist among varieties. In vitro, all of them inhibit colorectal cancer cell proliferation with Racimo variety in the top, and exercising a selective action on cancer cells by considering the lack of effects on CCD-18 cells. Furthermore, synergy was observed between olive oil and tomato carotenoids in inhibiting HT-29 cancer cell proliferation; conversely, phenolics showed no significant effects and hindered carotenoids actions.

http://www.ncbi.nlm.nih.gov/pubmed/27060896

“This report provides a theoretical basis for the concomitant [**synergistic**] use of P. fruticosa blended with green tea polyphenols, which can be effectively used as a compounded tea, dietary supplements, and substituent of synthetic antioxidant.”

Journal Of Food Science • May 2016

Synergistic Effects of Potentilla fruticosa L. Leaves Combined with Green Tea Polyphenols in a Variety of Oxidation Systems

Author information

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Abstract

Potentilla fruticosa L. leaves are widely used as tea in China, with many commercial “Jinlaomei” teas available in markets. It has been confirmed to possess significant antioxidant activity than that of butylated hydroxytoluene. In this study, the synergistic effects of P. fruticosa leaves extracts (PFE) combined with green tea polyphenols (GTP) were studied to elucidate their use in combination and find specific combinations with least concentrations that enhance the antioxidant activity. Isobolographic analysis indicated that the combination of PFE and GTP demonstrated extensive synergism (22/28 of the tests showed significant synergy) with 3:1 (PFE:GTP) exhibiting the best synergistic effect. Chemical compositions and content of 7 phenolic compounds in PFE, GTP, and their mixtures were evaluated by reverse-phase-high-performance liquid chromatography. While chemical composition did not seem to change after the combination, as no new peaks appeared in the chromatogram, and no existing peaks disappeared. However, the content of (+)-catechin, (-)-epigallocatechin (EGC), and , (-)-epigallocatechin gallate (EGCG) changed. Besides, antioxidant interactions of extracts and compounds were evaluated, EGC with hyperoside exhibited the greatest synergistic effect and the combination of 3:1 exhibited the strongest synergism (DPPH ß = 0.86, ABTS ß = 1.12, FRAP ß = 1.16). Therefore, interaction of phytochemicals may be one reason for the synergistic effects in PFE + GTP, with EGC + hyperoside likely playing an important role. This report provides a theoretical basis for the concomitant use of P. fruticosa blended with GTP, which can be effectively used as a compounded tea, dietary supplements, and substituent of synthetic antioxidant.

http://www.ncbi.nlm.nih.gov/pubmed/27061936

“Current topics of interest including **food synergy**, gut-brain interactions, nutritional phenotype and digestion in the elderly are considered.”

Journal Of The Science Of Food And Agriculture • May 2016

Human digestion - a processing perspective

Author information

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Abstract

The human digestive system is reviewed in the context of a process with four major unit operations: oral processing to reduce particle size and produce a bolus; gastric processing to initiate chemical and enzymatic breakdown; small intestinal processing to break down macromolecules and absorb nutrients; and fermentation and water removal in the colon. Topics are highlighted about which we need to know more, including effects of aging and dentition on particle size in the bolus, effects of different patterns of food and beverage intake on nutrition, changes in saliva production and composition, mechanical effects of gastric processing, distribution of pH in the stomach, physicochemical and enzymatic effects on nutrient availability and uptake in the small intestine, and the composition, effects of and changes in the microbiota of the colon. Current topics of interest including food synergy, gut-brain interactions, nutritional phenotype and digestion in the elderly are considered. Finally, opportunities for food design based on an understanding of digestive processing are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/26711173

“Foods, however, are complex combinations of nutrients and other compounds that act **synergistically** within the food and across food combinations.”

Advances In Nutrition • May 2016

Foods, Nutrients, and Dietary Patterns: Interconnections and Implications for Dietary Guidelines

Author information

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Abstract

Dietary guidelines provide evidence-based statements on food choices to meet nutritional requirements and reduce the risk of prevailing chronic disease. They involve a substantial amount of research translation, and their implementation has important health consequences. Foods, however, are complex combinations of nutrients and other compounds that act synergistically within the food and across food combinations. In addition, the evidence base underpinning dietary guidelines accesses research that reflects different study designs, with inherent strengths and limitations. We propose a systematic approach for the review of evidence that begins with research on dietary patterns. This research will identify the combinations of foods that best protect, or appear deleterious to, health. Next, we suggest that evidence be sought from research that focuses on the effects of individual foods. Finally, nutrient-based research should be considered to explain the mechanisms by which these foods and dietary patterns exert their effects, take into account the effects of ingredients added to the food supply, and enable assessments of dietary sufficiency. The consideration of individual nutrients and food components (e.g., upper limits for saturated fat, added sugar, and sodium) provides important benchmarks for evaluating overall diet quality. The concepts of core and discretionary foods (nutrient-rich and nutrient-poor foods, respectively) enable distinctions between foods, and this has implications for the relation between food policy and food manufacturing. In summary, evidence supporting healthy dietary patterns provides the foundation for the development of dietary guidelines. Further reference to individual foods and nutrients follows from the foundation of healthy dietary patterns.

http://www.ncbi.nlm.nih.gov/pubmed/27184272

“Dietary components in combination may act **synergistically** and produce enhanced biological activities.”

Journal Of Food Science • May 2016

Enhanced Anti-Inflammatory Activities by the Combination of Luteolin and Tangeretin

Author information

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Abstract

Dietary components in combination may act synergistically and produce enhanced biological activities. Herein, we investigated the anti-inflammatory effects of 2 flavonoids, that is luteolin (LUT) and tangeretin (TAN) in combination. Lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages were treated with noncytotoxic concentrations of LUT, TAN, and their combinations. The results showed that LUT/TAN in combination produced synergistic inhibitory effects on LPS-stimulated production of nitric oxide (NO). ELISA results demonstrated that LUT/TAN in combination caused stronger suppression on the LPS-induced overexpression of proinflammatory mediators, such as prostaglandin E2 (PGE2), interleukin (IL)-1ß, and IL-6 than LUT or TAN alone. Immunoblotting and Real-Time PCR analyses showed that LUT/TAN combination significantly decreased LPS-induced protein and mRNA expression of inducible nitric oxide synthase and cyclooxygenase-2. These inhibitory effects of the combination treatment were stronger than those produced by LUT or TAN alone. Overall, our results demonstrated for the first time that combination of LUT and TAN produced synergistic anti-inflammatory effects in LPS-stimulated RAW 264.7 macrophages.

http://www.ncbi.nlm.nih.gov/pubmed/27095513

“In this review article, we highlight multiple molecular targets responsible for the anticancer mechanism of capsaicin. In addition, we deal with the benefits of combinational use of capsaicin with other dietary or chemotherapeutic compounds, focusing on **synergistic** anticancer activities.”

Anticancer Research • June 2016

Anticancer Properties of Capsaicin Against Human Cancer

By Ruth Clark and Seong-Ho Lee

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Abstract

There is persuasive epidemiological and experimental evidence that dietary phytochemicals have anticancer activity. Capsaicin is a bioactive phytochemical abundant in red and chili peppers. While the preponderance of the data strongly indicates significant anticancer benefits of capsaicin, more information to highlight molecular mechanisms of its action is required to improve our knowledge to be able to propose a potential therapeutic strategy for use of capsaicin against cancer. Capsaicin has been shown to alter the expression of several genes involved in cancer cell survival, growth arrest, angiogenesis and metastasis. Recently, many research groups, including ours, found that capsaicin targets multiple signaling pathways, oncogenes and tumor- suppressor genes in various types of cancer models. In this review article, we highlight multiple molecular targets responsible for the anticancer mechanism of capsaicin. In addition, we deal with the benefits of combinational use of capsaicin with other dietary or chemotherapeutic compounds, focusing on synergistic anticancer activities.

http://ar.iiarjournals.org/content/36/3/837.full.pdf+html

“Food and nutrition insecurity was associated with the presence of cardiometabolic risk factors in the assessed publications. Childhood and adolescence constitute a period of life that is vulnerable to food insecurity consequences, making it extremely important to ensure the regular and permanent access to food. Because this is a complex association, some difficulties are found, such as the **synergy** between risk factors, the assessment of heterogeneous groups and extrapolation of data to other populations, in addition to the influence of environmental factors.”

Revista Paulista de Pediatria • June 2016

Association between food and nutrition insecurity with cardiometabolic risk factors in childhood and adolescence: a systematic review

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Abstract

OBJECTIVE
To address the association between food and nutrition insecurity and cardiometabolic risk factors in childhood and adolescence.

DATA SOURCE
Articles were selected from the Medline, Lilacs and SciELO databases with no publication date limit, involving children and adolescents, using the descriptors: food and nutrition security, diabetes mellitus, hypertension, metabolic syndrome, stress and dyslipidemia. The terms were used in Portuguese, English and Spanish. The search was carried out systematically and independently by two reviewers.

DATA SYNTHESIS
Exposure to food insecurity during childhood and adolescence ranged from 3.3% to 82% in the selected publications. Exposure to food insecurity was associated with stress, anxiety, greater chance of hospitalization, nutritional deficiencies, excess weight and inadequate diets with reduced intake of fruits and vegetables and increased consumption of refined carbohydrates and fats.

CONCLUSIONS
Food and nutrition insecurity was associated with the presence of cardiometabolic risk factors in the assessed publications. Childhood and adolescence constitute a period of life that is vulnerable to food insecurity consequences, making it extremely important to ensure the regular and permanent access to food. Because this is a complex association, some difficulties are found, such as the synergy between risk factors, the assessment of heterogeneous groups and extrapolation of data to other populations, in addition to the influence of environmental factors.

http://www.ncbi.nlm.nih.gov/pubmed/26564327

Journal Of Neuroscience Research • June 2016

Cerebral hypoperfusion and glucose hypometabolism: Key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease

By M.A. Daulatzai

Abstract

"**Aging, hypertension, diabetes, hypoxia/obstructive sleep apnea (OSA), obesity, vitamin B12/folate deficiency, depression, and traumatic brain injury synergistically promote diverse pathological mechanisms including cerebral hypoperfusion and glucose hypometabolism. These risk factors trigger neuroinflammation and oxidative-nitrosative stress that in turn decrease nitric oxide and enhance endothelin, Amyloid-ß deposition, cerebral amyloid angiopathy, and blood-brain barrier disruption.** Proinflammatory cytokines, endothelin-1, and oxidative-nitrosative stress trigger several pathological feedforward and feedback loops. These upstream factors persist in the brain for decades, upregulating amyloid and tau, before the cognitive decline. These cascades lead to neuronal Ca2+ increase, neurodegeneration, cognitive/memory decline, and Alzheimer's disease (AD). However, strategies are available to attenuate cerebral hypoperfusion and glucose hypometabolism and ameliorate cognitive decline. AD is the leading cause of dementia among the elderly. There is significant evidence that pathways involving inflammation and oxidative-nitrosative stress (ONS) play a key pathophysiological role in promoting cognitive dysfunction. Aging and several comorbid conditions mentioned above promote diverse pathologies. These include inflammation, ONS, hypoperfusion, and hypometabolism in the brain. In AD, chronic cerebral hypoperfusion and glucose hypometabolism precede decades before the cognitive decline. **These comorbid disease conditions may share and synergistically activate these pathophysiological pathways.** Inflammation upregulates cerebrovascular pathology through proinflammatory cytokines, endothelin-1, and nitric oxide (NO). Inflammation-triggered ONS promotes long-term damage involving fatty acids, proteins, DNA, and mitochondria; these amplify and perpetuate several feedforward and feedback pathological loops. The latter includes dysfunctional energy metabolism (compromised mitochondrial ATP production), amyloid-ß generation, endothelial dysfunction, and blood-brain-barrier disruption. These lead to decreased cerebral blood flow and chronic cerebral hypoperfusion- that would modulate metabolic dysfunction and neurodegeneration. In essence, hypoperfusion deprives the brain from its two paramount trophic substances, viz., oxygen and nutrients. Consequently, the brain suffers from synaptic dysfunction and neuronal degeneration/loss, leading to both gray and white matter atrophy, cognitive dysfunction, and AD. This Review underscores the importance of treating the above-mentioned comorbid disease conditions to attenuate inflammation and ONS and ameliorate decreased cerebral blood flow and hypometabolism. Additionally, several strategies are described here to control chronic hypoperfusion of the brain and enhance cognition."

http://www.ncbi.nlm.nih.gov/pubmed/27350397

“Many neurological diseases, including autism, depression, dementia, anxiety disorder and Parkinson’s disease, are associated with abnormal sleep patterns, which are directly linked to pineal gland dysfunction. The pineal gland is highly susceptible to environmental toxicants. Two pervasive substances in modern industrialized nations are aluminum and glyphosate, the active ingredient in the herbicide, Roundup®. In this paper, we show how these two toxicants work **synergistically** to induce neurological damage.”

Agricultural Science • January 2015

Aluminum and Glyphosate Can Synergistically Induce Pineal Gland Pathology: Connection to Gut Dysbiosis and Neurological Disease

by Stephanie Seneff1*, Nancy Swanson2, Chen Li1

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Abstract

Many neurological diseases, including autism, depression, dementia, anxiety disorder and Parkinson’s disease, are associated with abnormal sleep patterns, which are directly linked to pineal gland dysfunction. The pineal gland is highly susceptible to environmental toxicants. Two pervasive substances in modern industrialized nations are aluminum and glyphosate, the active ingredient in the herbicide, Roundup®. In this paper, we show how these two toxicants work synergistically to induce neurological damage. Glyphosate disrupts gut bacteria, leading to an overgrowth of Clostridium difficile. Its toxic product, p-cresol, is linked to autism in both human and mouse models. p-Cresol enhances uptake of aluminum via transferrin. Anemia, a result of both aluminum disruption of heme and impaired heme synthesis by glyphosate, leads to hypoxia, which induces increased pineal gland transferrin synthesis. Premature birth is associated with hypoxic stress and with substantial increased risk to the subsequent development of autism, linking hypoxia to autism. Glyphosate chelates aluminum, allowing ingested aluminum to bypass the gut barrier. This leads to anemia-induced hypoxia, promoting neurotoxicity and damaging the pineal gland. Both glyphosate and aluminum disrupt cytochrome P450 enzymes, which are involved in melatonin metabolism. Furthermore, melatonin is derived from tryptophan, whose synthesis in plants and microbes is blocked by glyphosate. We also demonstrate a plausible role for vitamin D3 dysbiosis in impaired gut function and impaired serotonin synthesis. This paper proposes that impaired sulfate supply to the brain mediates the damage induced by the synergistic action of aluminum and glyphosate on the pineal gland and related midbrain nuclei.

www.scirp.org/journal/Paperinformation.aspx?PaperID=53106

“The display of **synergy** or antagonism by the composite herbal extracts in ameliorating hyperglycemia and dyslipidemia depended on the type and number of individual herbal extract used in constituting the experimental herbal formulations.”

Journal Of Traditional And Complementary Medicine • February 2015

Blood glucose level and lipid profile of alloxan-induced hyperglycemic rats treated with single and combinatorial herbal formulations

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Abstract

The current study sought to investigate the capacities of single and combinatorial herbal formulations of leaf extracts of Acanthus montanus, Asystasia gangetica, Emilia coccinea, and Hibiscus rosasinensis to reverse hyperglycemia and dyslipidemia in alloxan-induced diabetic male rats. Phytochemical composition of the herbal extracts, fasting plasma glucose concentration (FPGC), and serum lipid profile (SLP) of the rats were measured by standard methods. The relative abundance of phytochemicals in the four experimental leaf extracts was in the following order: flavonoids > alkaloids > saponins > tannins. Hyperglycemic rats (HyGR) treated with single and combinatorial herbal formulations showed evidence of reduced FPGC compared with the untreated HyGR and were normoglycemic (FPGC < 110.0 mg/dL). Similarly, HyGR treated with single and combinatorial herbal formulations showed evidence of readjustments in their SLPs. Generally, HyGR treated with triple herbal formulations (THfs) exhibited the highest atherogenic index compared with HyGR treated with single herbal formulations (SHfs), double herbal formulations (DHfs), and quadruple herbal formulation (QHf). The display of synergy or antagonism by the composite herbal extracts in ameliorating hyperglycemia and dyslipidemia depended on the type and number of individual herbal extract used in constituting the experimental herbal formulations. Furthermore, the capacities of the herbal formulations (SHfs, DHfs, THfs, and QHf) to exert glycemic control and reverse dyslipidemia did not follow predictable patterns in the animal models.

Full text, graphs, charts and 95 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4833464/

Environmental Toxicology And Pharmacology • March 2015

Synergistic effect of non-ionic surfactants Tween 80 and PEG6000 on cytotoxicity of insecticides

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Abstract

“The use of surfactants in the development of a suitable formulation for insecticides should improve the solubility behavior, the permeability and the efficiency against pests meanwhile decrease the toxic risks of insecticides on human health. Cytotoxicity of insecticides including abamectin, chlorfluazuron, hexaflumuron, chlorpyrifos, and tebufenozide was assessed on human HepG2 and lepidopteran Tn5B1-4 cells utilizing insecticide alone and in combination with nontoxic concentrations of nonionic surfactants Tween 80 and PEG6000. The results showed avermection revealed high cytotoxicity, chlorfluazuron and hexaflumuron possessed median cytotoxicity, and chlorpyrifos and tebufenozide had little cytotoxicity on HepG2 and Tn5B1-4 cells. The co-incubation with Tween 80 and PEG6000 powerfully counteracted the cytotoxicity of avermectin. Tween 80 enhanced, whereas PEG6000 compressed, the cytotoxicity of chlorfluazuron on Tn5B1-4 cells, and also improved a bit of the cytotoxicity of chlorpyrifos or tebufenozide on HepG2 cells. PEG6000 was more suitable to be used as surfactant in improving insecticide solubility and reducing the cytotoxicity. The present investigation demonstrates the necessity of utilizing surfactants to weaken the cytotoxicity of insecticides.”

http://www.ncbi.nlm.nih.gov/pubmed/25699500

“... the concept of food **synergy** within the Mediterranean Diet encourages future trials that evaluate the impact of comprehensive lifestyle patterns to help maintaining cognitive functions into old age.”

Frontiers In Aging And Neuroscience • July 2015

Components of a Mediterranean diet and their impact on cognitive functions in aging

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Abstract

BACKGROUND

Adhering to the Mediterranean diet (MeDi) is known to be beneficial with regard to many age-associated diseases including cardiovascular diseases and type 2 diabetes. Recent studies also suggest an impact on cognition and brain structure, and increasing effort is made to track effects down to single nutrients.

AIMS

We aimed to review whether two MeDi components, i.e., long-chain omega-3 fatty acids (LC-n3-FA) derived from sea-fish, and plant polyphenols including resveratrol (RSV), exert positive effects on brain health in aging.

CONTENT

We summarized health benefits associated with the MeDi and evaluated available studies on the effect of (1) fish-consumption and LC-n3-FA supplementation as well as (2) diet-derived or supplementary polyphenols such as RSV, on cognitive performance and brain structure in animal models and human studies. Also, we discussed possible underlying mechanisms.

CONCLUSION

A majority of available studies suggest that consumption of LC-n3-FA with fish or fish oil-supplements exerts positive effects on brain health and cognition in older humans. However, more large-scale randomized controlled trials are needed to draw definite recommendations. Considering polyphenols and RSV, only few controlled studies are available to date, yet the evidence based on animal research and first interventional human trials is promising and warrants further investigation. In addition, the concept of food synergy within the MeDi encourages future trials that evaluate the impact of comprehensive lifestyle patterns to help maintaining cognitive functions into old age.

Full text, graphs, charts and 99 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4495334/

Critical Reviews In Food, Science And Nutrition • July 2015

Dietary Antioxidant Synergy in Chemical and Biological Systems

Author information

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Abstract

"Antioxidant (AOX) **synergies** have been much reported in chemical ("test-tube" based assays focusing on pure chemicals), biological (tissue culture, animal and clinical models), and food systems during the past decade. Tentative **synergies** differ from each other due to the composition of AOX and the quantification methods. Regeneration mechanism responsible for **synergy** in chemical systems has been discussed. Solvent effects could contribute to the artefacts of **synergy** observed in the chemical models. **Synergy** in chemical models may hardly be relevant to biological systems which have been much less studied. Apparent discrepancies exist in understanding the molecular mechanisms in both chemical and biological systems. This review discusses diverse variables associated with AOX **synergy** and molecular scenarios for explanation. Future research to better utilize the **synergy** is suggested."

http://www.ncbi.nlm.nih.gov/pubmed/26176981

“Combined Sulforaphane and selenium treatment resulted in a **synergistic** up-regulation of TrxR-1 that in part contributed to the enhanced protection against free radical-mediated cell death provided by the cotreatment.”

Nutrition Research • July 2015

Synergy between sulforaphane and selenium in protection against oxidative damage in colonic CCD841 cells

Author information

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Abstract

Dietary isothiocyanates are potent inducers of the NF-E2-related factor 2 (Nrf2) pathway. Sulforaphane (SFN), a representative dietary isothiocyanate, has previously been shown to up-regulate antioxidant enzymes such as selenium (Se)-dependent thioredoxin reductase-1 (TrxR-1) in many tumor cell lines. In the present study, we hypothesized that a combination of SFN and Se would have a synergistic effect on the up-regulation of TrxR-1 and the protection against oxidative damage in the normal colonic cell line CCD841. Treatment of cells with SFN and Se significantly induced TrxR-1 expression. Pretreatment of cells with SFN protects against H2O2-induced cell death; this protection was enhanced by cotreatment with Se. The small interfering RNA knockdown of either TrxR-1 or Nrf2 reduced the protection afforded by SFN and Se cotreatment; TrxR-1 and Nrf2 knockdown reduced cell viabilities to 66.5% and 51.1%, respectively, down from 82.4% in transfection-negative controls. This suggests that both TrxR-1 and Nrf2 are important in SFN-mediated protection against free radical-induced cell death. Moreover, flow cytometric analysis showed that TrxR-1 and Nrf2 were involved in SFN-mediated protection against H2O2-induced apoptosis. In summary, SFN activates the Nrf2 signaling pathway and protects against H2O2-mediated oxidative damage in normal colonic cells. Combined SFN and Se treatment resulted in a synergistic up-regulation of TrxR-1 that in part contributed to the enhanced protection against free radical-mediated cell death provided by the cotreatment.

http://www.ncbi.nlm.nih.gov/pubmed/26094214

“The **synergistic** antimicrobial effects between berberine chloride and totarol were observed in all tested strains grown in biofilms using a chequerboard microdilution method, with the fractional inhibitory concentration index values ranging from 0.125 to 0.375.”

Journal Of Medical Microbiology • August 2015

The synergy of berberine chloride and totarol against Staphylococcus aureus grown in planktonic and biofilm cultures

Author information

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Abstract

Staphylococcus aureus (S. aureus) is commonly associated with hospital-acquired infections and is known to form biofilms. Bacteria inside biofilms display an increased resistance to chemotherapeutics and host immune defences. Efficient antibiotics or combination therapy are urgently needed to treat patients with biofilm-associated MRSA infections. The objective of the current study was to evaluate the in vitro antimicrobial activities of totarol alone or in combination with berberine chloride (BBR) against S. aureus grown in planktonic and biofilm cultures. The synergistic antimicrobial effects between BBR and totarol were observed in all tested strains grown in biofilms using a chequerboard microdilution method, with the fractional inhibitory concentration index values ranging from 0.125 to 0.375. No antagonistic activity was observed in any of the strains tested in suspension or biofilm cultures. The synergistic activity against S. aureus biofilms was also corroborated by confocal laser scanning microscopy and adhesion assays. Moreover, the present study demonstrated that combination BBR and totarol treatment effectively decreased the formation of S. aureus biofilms by affecting extracellular genomic DNA release and polysaccharide intercellular adhesin expression. Subsequently, real-time reverse transcriptase PCR analysis revealed that the combination of BBR and totarol effectively inhibited the transcription of the biofilm-related genes sarA, cidA and icaA. These results suggest that the combination of totarol and BBR is momentous for the further development of a therapy protocol against S. aureus biofilms.

http://www.ncbi.nlm.nih.gov/pubmed/26272283

“**Synergy Maps** improve the state of the art in compound combination visualization, by simultaneously representing individual compound properties and their interactions. The web-based tool allows straightforward exploration of combination data, and easier identification of correlations between compound properties and interactions.”

Journal Cheminform • August 2015

Synergy Maps: exploring compound combinations using network-based visualization

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Abstract

BACKGROUND

The phenomenon of super-additivity of biological response to compounds applied jointly, termed synergy, has the potential to provide many therapeutic benefits. Therefore, high throughput screening of compound combinations has recently received a great deal of attention. Large compound libraries and the feasibility of all-pairs screening can easily generate large, information-rich datasets. Previously, these datasets have been visualized using either a heat-map or a network approach-however these visualizations only partially represent the information encoded in the dataset.

RESULTS

A new visualization technique for pairwise combination screening data, termed “Synergy Maps”, is presented. In a Synergy Map, information about the synergistic interactions of compounds is integrated with information about their properties (chemical structure, physicochemical properties, bioactivity profiles) to produce a single visualization. As a result the relationships between compound and combination properties may be investigated simultaneously, and thus may afford insight into the synergy observed in the screen. An interactive web app implementation, available at http://richlewis42.github.io/synergy-maps, has been developed for public use, which may find use in navigating and filtering larger scale combination datasets. This tool is applied to a recent all-pairs dataset of anti-malarials, tested against Plasmodium falciparum, and a preliminary analysis is given as an example, illustrating the disproportionate synergism of histone deacetylase inhibitors previously described in literature, as well as suggesting new hypotheses for future investigation.

Full text, graphs, charts and 49 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4521339/

JAMA Ophthalmology • October 2015

Association between vitamin D status and age-related macular degeneration by genetic risk

Author information

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Abstract

IMPORTANCE

Deficient 25-hydroxyvitamin D (25[OH]D) concentrations have been associated with increased odds of age-related macular degeneration (AMD).

OBJECTIVE

To examine whether this association is modified by genetic risk for AMD and whether there is an association between AMD and single-nucleotide polymorphisms of genes involved in vitamin D transport, metabolism, and genomic function.

DESIGN, SETTING, AND PARTICIPANTS

Postmenopausal women (N=913) who were participants of the Carotenoids in Age-Related Eye Disease Study (CAREDS) (aged 54 to <75 years) with available serum 25(OH)D concentrations (assessed October 1, 1993, to December 31, 1998), genetic data, and measures of AMD (n=142) assessed at CAREDS baseline from May 14, 2001, through January 31, 2004, were studied.

MAIN OUTCOMES AND MEASURES

Prevalent early or late AMD was determined from graded, stereoscopic fundus photographs. Logistic regression was used to estimate odds ratios (ORs) and 95% CIs for AMD by the joint effects of 25(OH)D (<12, ≥12 to <20, ≥20 to <30, and ≥30 ng/mL) and risk genotype (noncarrier, 1 risk allele, or 2 risk alleles). The referent group was noncarriers with adequate vitamin D status (≥30 ng/mL). Joint effect ORs were adjusted for age, smoking, iris pigmentation, self-reported cardiovascular disease, self-reported diabetes status, and hormone use. Additive and multiplicative interactions were assessed using the synergy index (SI) and an interaction term, respectively. To examine the association between AMD and variants in vitamin D-related genes, age-adjusted ORs and 95% CIs were estimated using logistic regression.

RESULTS

Among the 913 women, 550 had adequate levels of vitamin D (≥20 ng/mL), 275 had inadequate levels (≥12 to <20 mg/mL), and 88 had deficient levels (<12 ng/mL). A 6.7-fold increased odds of AMD (95% CI, 1.6-28.2) was observed among women with deficient vitamin D status (25[OH]D <12 ng/mL) and 2 risk alleles for CFH Y402H (SI for additive interaction, 1.4; 95% CI, 1.1-1.7; P for multiplicative interaction=.25). Significant additive (SI, 1.4; 95% CI, 1.1-1.7) and multiplicative interactions (P=.02) were observed for deficient women with 2 high-risk CFI (rs10033900) alleles (OR, 6.3; 95% CI, 1.6-24.2). The odds of AMD did not differ by genotype of candidate vitamin D genes.

CONCLUSIONS AND RELEVANCE

"In this study, the odds of age-related macular degeneration were highest in those with deficient vitamin D status and 2 risk alleles for the CFH and CFI genotypes, suggesting a **synergistic** effect between vitamin D status and complement cascade protein function. Limited sample size led to wide CIs. Findings may be due to chance or explained by residual confounding."

Full text, graphs, charts and 71 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4841267/

“**Synergy** was evident for two endpoints (nuclear intensity and mitochondrial mass) at concentrations contaminating maize above legal limits ... The study introduces for the first time, a holistic approach to identify the impact in terms of toxicity to humans when multiple chemical contaminants are present in foodstuffs. Governmental regulatory bodies must begin to contemplate how to safeguard the population when such mixtures of contaminants are found in foods and this study starts to address this critical issue.”

Toxicology Letters • October 2015

Challenging conventional risk assessment with respect to human exposure to multiple food contaminants in food: A case study using maize

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Abstract

Mycotoxins and heavy metals are ubiquitous in the environment and contaminate many foods. The widespread use of pesticides in crop production to control disease contributes further to the chemical contamination of foods. Thus multiple chemical contaminants threaten the safety of many food commodities; hence the present study used maize as a model crop to identify the severity in terms of human exposure when multiple contaminants are present. High Content Analysis (HCA) measuring multiple endpoints was used to determine cytotoxicity of complex mixtures of mycotoxins, heavy metals and pesticides. Endpoints included nuclear intensity (NI), nuclear area (NA), plasma membrane permeability (PMP), mitochondrial membrane potential (MMP) and mitochondrial mass (MM). At concentrations representing legal limits of each individual contaminant in maize (3ng/ml ochratoxin A (OTA), 1µg/ml fumonisin B1 (FB1), 2ng/ml aflatoxin B1 (AFB1), 100ng/ml cadmium (Cd), 150ng/ml arsenic (As), 50ng/ml chlorpyrifos (CP) and 5µg/ml pirimiphos methyl (PM), the mixtures (tertiary mycotoxins plus Cd/As) and (tertiary mycotoxins plus Cd/As/CP/PM) were cytotoxic for NA and MM endpoints with a difference of up to 13.6% ($p \leq 0.0001$) and 12% ($p \leq 0.0001$) respectively from control values. The most cytotoxic mixture was (tertiary mycotoxins plus Cd/As/CP/PM) across all 4 endpoints (NA, NI, MM and MMP) with increases up to 61.3%, 23.0%, 61.4% and 36.3% ($p \leq 0.0001$) respectively. Synergy was evident for two endpoints (NI and MM) at concentrations contaminating maize above legal limits, with differences between expected and measured values of (6.2-12.4% ($p \leq 0.05$-$p \leq 0.001$) and 4.5-12.3% ($p \leq 0.05$-$p \leq 0.001$) for NI and MM, respectively. The study introduces for the first time, a holistic approach to identify the impact in terms of toxicity to humans when multiple chemical contaminants are present in foodstuffs. Governmental regulatory bodies must begin to contemplate how to safeguard the population when such mixtures of contaminants are found in foods and this study starts to address this critical issue.

http://www.ncbi.nlm.nih.gov/pubmed/26196220

“There was some specificity as certain fungi were unaffected. There was no **synergy** against bacterial or mammalian cells. The results indicate that translation fidelity is a promising new target for combinatorial treatment of undesirable fungi, the combinations requiring substantially decreased doses of active components compared to each agent alone.”

Science Reports • November 2015

Novel, Synergistic Antifungal Combinations that Target Translation Fidelity

Author information

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Abstract

There is an unmet need for new antifungal or fungicide treatments, as resistance to existing treatments grows. Combination treatments help to combat resistance. Here we develop a novel, effective target for combination antifungal therapy. Different aminoglycoside antibiotics combined with different sulphate-transport inhibitors produced strong, synergistic growth-inhibition of several fungi. Combinations decreased the respective MICs by ≥8-fold. Synergy was suppressed in yeast mutants resistant to effects of sulphate-mimetics (like chromate or molybdate) on sulphate transport. By different mechanisms, aminoglycosides and inhibition of sulphate transport cause errors in mRNA translation. The mistranslation rate was stimulated up to 10-fold when the agents were used in combination, consistent with this being the mode of synergistic action. A range of undesirable fungi were susceptible to synergistic inhibition by the combinations, including the human pathogens Candida albicans, C. glabrata and Cryptococcus neoformans, the food spoilage organism Zygosaccharomyces bailii and the phytopathogens Rhizoctonia solani and Zymoseptoria tritici. There was some specificity as certain fungi were unaffected. There was no synergy against bacterial or mammalian cells. The results indicate that translation fidelity is a promising new target for combinatorial treatment of undesirable fungi, the combinations requiring substantially decreased doses of active components compared to each agent alone.

Full text, graphs, charts and 36 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4648087/

Ophthalmology • November 2015

Joint Associations of Diet, Lifestyle, and Genes with Age-Related Macular Degeneration

Author information

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Abstract

PURPOSE

Unhealthy lifestyles have been associated with increased odds for age-related macular degeneration (AMD). Whether this association is modified by genetic risk for AMD is unknown and was investigated.

DESIGN

Interactions between healthy lifestyles AMD risk genotypes were studied in relation to the prevalence of AMD, assessed 6 years later.

PARTICIPANTS

Women 50 to 79 years of age in the Carotenoids in Age-Related Eye Disease Study with exposure and AMD data (n=1663).

METHODS

Healthy lifestyle scores (0-6 points) were assigned based on Healthy Eating Index scores, physical activity (metabolic equivalent of task hours/week), and smoking pack years assessed in 1994 and 1998. Genetic risk was based on Y402H in complement factor H (CFH) and A69S in age-related maculopathy susceptibility locus 2 (ARMS2). Additive and multiplicative interactions in odds ratios were assessed using the synergy index and a multiplicative interaction term, respectively.

MAIN OUTCOME MEASURES

AMD presence and severity were assessed from grading of stereoscopic fundus photographs taken in 2001-2004. AMD was present in 337 women, 91% of whom had early AMD.

RESULTS

The odds of AMD were 3.3 times greater (95% confidence interval [CI], 1.8-6.1) in women with both low healthy lifestyle score (0-2) and high-risk CFH genotype (CC), relative to those who had low genetic risk (TT) and high healthy lifestyle scores (4-6). There were no significant additive (synergy index [SI], 1.08; 95% CI, 0.70-1.67) or multiplicative (Pinteraction=0.94) interactions in the full sample. However, when limiting the sample to women with stable diets before AMD assessment (n=728) the odds for AMD associated with low healthy lifestyle scores and high-risk CFH genotype were strengthened (odds ratio, 4.6; 95% CI, 1.8-11.6) and the synergy index was significant (SI, 1.34; 95% CI, 1.05-1.70). Adjusting for dietary lutein and zeaxanthin attenuated, and therefore partially explained, the joint association. There were no significant additive or multiplicative interactions for ARMS2 and lifestyle score.

CONCLUSIONS

“Having unhealthy lifestyles and 2 CFH risk alleles increased age-related macular degeneration risk (primarily in the early stages), in an or additive or greater (**synergistic**) manner. However, unhealthy lifestyles increased age-related macular degeneration risk regardless of age-related macular degeneration risk genotype.”

http://www.ncbi.nlm.nih.gov/pubmed/26354764

PLoS One • May 2014

Quantifying synergy: a systematic review of mixture toxicity studies within environmental toxicology

Author information

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Abstract

Cocktail effects and synergistic interactions of chemicals in mixtures are an area of great concern to both the public and regulatory authorities. The main concern is whether some chemicals can enhance the effect of other chemicals, so that they jointly exert a larger effect than predicted. This phenomenon is called synergy. Here we present a review of the scientific literature on three main groups of environmentally relevant chemical toxicants: pesticides, metal ions and antifouling compounds. The aim of the review is to determine 1) the frequency of synergy, 2) the extent of synergy, 3) whether any particular groups or classes of chemicals tend to induce synergy, and 4) which physiological mechanisms might be responsible for this synergy. Synergy is here defined as mixtures with minimum two-fold difference between observed and predicted effect concentrations using Concentration Addition (CA) as a reference model and including both lethal and sub-lethal endpoints. The results showed that synergy occurred in 7%, 3% and 26% of the 194, 21 and 136 binary pesticide, metal and antifoulants mixtures included in the data compilation on frequency. The difference between observed and predicted effect concentrations was rarely more than 10-fold. For pesticides, synergistic mixtures included cholinesterase inhibitors or azole fungicides in 95% of 69 described cases. Both groups of pesticides are known to interfere with metabolic degradation of other xenobiotics. For the four synergistic metal and 47 synergistic antifoulant mixtures the pattern in terms of chemical groups inducing synergy was less clear. Hypotheses in terms of mechanisms governing these interactions are discussed. It was concluded that true synergistic interactions between chemicals are rare and often occur at high concentrations. Addressing the cumulative rather than synergistic effect of co-occurring chemicals, using standard models as CA, is therefore regarded as the most important step in the risk assessment of chemical cocktails.

Full text, graphs, charts and 90 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4008607/

“Both groups of pesticides are known to interfere with metabolic degradation of other xenobiotics.

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“We demonstrated that binary mixtures of both chemicals induce greater cytotoxic effects than those reported after single exposure to each compound [alone].”

Food Chemistry Toxicology • October 2014

The antioxidant butylated hydroxyanisole potentiates the toxic effects of propylparaben in cultured mammalian cells

Author information

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Abstract

Butylated hydroxyanisole and propylparaben are phenolic preservatives commonly used in food, pharmaceutical and personal care products. Both chemicals have been subjected to extensive toxicological studies, due to the growing concern regarding their possible impacts on environmental and human health. However, the cytotoxicity and underlying mechanisms of co-exposure to these compounds have not been explored. In this study, a set of relevant cytotoxicity endpoints including cell viability and proliferation, oxidative stress, DNA damage and gene expression changes were analyzed to assess whether the antioxidant butylated hydroxyanisole could prevent the pro-oxidant effects caused by propylparaben in Vero cells. We demonstrated that binary mixtures of both chemicals induce greater cytotoxic effects than those reported after single exposure to each compound. Simultaneous treatment with butylated hydroxyanisole and propylparaben caused G0/G1 cell cycle arrest as a result of enhanced generation of oxidative stress and DNA double strand breaks. DNA microarray analysis revealed that a cross-talk between transforming growth factor beta (TGFß) and ataxia-telangiectasia mutated kinase (ATM) pathways regulates the response of Vero cells to the tested compounds in binary mixture. Our findings indicate that butylated hydroxyanisole potentiates the pro-oxidant effects of propylparaben in cultured mammalian cells and provide useful information for their safety assessment.

http://www.ncbi.nlm.nih.gov/pubmed/25086368

“More and more evidence suggests that the health benefits of fruits, vegetables, whole grains, and other plant foods are attributed to the **synergy** or interactions of bioactive compounds and other nutrients in whole foods.”

Advances In Nutrition • May 2013

Health-promoting components of fruits and vegetables in the diet

By R.H. Liu

Abstract

Regular consumption of fruits, vegetables, whole grains, and other plant foods has been negatively correlated with the risk of the development of chronic diseases. There is a huge gap between the average consumption of fruits and vegetables in Americans and the amount recommended by the 2010 Dietary Guidelines for Americans. The key is to encourage consumers to increase the total amount to 9 to 13 servings of fruits and vegetables in all forms available. Fresh, processed fruits and vegetables including frozen and canned, cooked, 100% fruit juices and 100% vegetable juices, as well as dry fruits are all considered as servings of fruits and vegetables per day. A wide variety of fruits, vegetables, whole grains, and other plant foods provide a range of nutrients and different bioactive compounds including phytochemicals, vitamins, minerals, and fibers. Potatoes serve as one of the low-fat foods with unique nutrients and phytochemical profiles, particularly rich in vitamin C, vitamin B-6, potassium, manganese, and dietary fibers. Potatoes provide 25% of vegetable phenolics in the American diet, the largest contributors among the 27 vegetables commonly consumed in the United States, including flavonoids (quercetin and kaempferol), phenolic acids (chlorogenic acid and caffeic acid), and carotenoids (lutein and zeaxanthin). More and more evidence suggests that the health benefits of fruits, vegetables, whole grains, and other plant foods are attributed to the synergy or interactions of bioactive compounds and other nutrients in whole foods. Therefore, consumers should obtain their nutrients, antioxidants, bioactive compounds, and phytochemicals from a balanced diet with a wide variety of fruits, vegetables, whole grains, and other plant foods for optimal nutrition, health, and well-being, not from dietary supplements.

Full text with 68 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3650511/

Critical Reviews In Food Science And Nutrition • July 2013

Dried plums and their products: composition and health effects—an updated review

Author information

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Abstract

"This paper describes composition of dried plums and their products (prune juice and dried plum powder) with special attention to possibly bioactive compounds. Dried plums contain significant amounts of sorbitol, quinic acid, chlorogenic acids, vitamin K1, boron, copper, and potassium. **Synergistic** action of these and other compounds, which are also present in dried plums in less conspicuous amounts, may have beneficial health effects when dried plums are regularly consumed. Snacking on dried plums may increase satiety and reduce the subsequent intake of food, helping to control obesity, diabetes, and related cardiovascular diseases. Despite their sweet taste, dried plums do not cause large postprandial rise in blood glucose and insulin. Direct effects in the gastrointestinal tract include prevention of constipation and possibly colon cancer. The characteristic phenolic compounds and their metabolites may also act as antibacterial agents in both gastrointestinal and urinary tracts. The indirect salutary effects on bone turnover are supported by numerous laboratory studies with animals and cell cultures. Further investigation of phenolic compounds in dried plums, particularly of high molecular weight polymers, their metabolism and biological actions, alone and in **synergy** with other dried plum constituents, is necessary to elucidate the observed health effects and to indicate other benefits."

http://www.ncbi.nlm.nih.gov/pubmed/24090144

Critical Reviews In Toxicology • May 2011

Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment

Author information
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Abstract

“There is increasing interest in the use of tiered approaches in risk assessment of mixtures or co-exposures to chemicals for prioritization. One possible screening-level risk assessment approach is the threshold of toxicological concern (TTC). To date, default assumptions of dose or response additivity have been used to characterize the toxicity of chemical mixtures. Before a screening-level approach could be used, it is essential to know whether **synergistic** interactions can occur at low, environmentally relevant exposure levels. Studies demonstrating **synergism** in mammalian test systems were identified from the literature, with emphasis on studies performed at doses close to the points of departure (PODs) for individual chemicals. This search identified 90 studies on mixtures. Few included quantitative estimates of low-dose **synergy**; calculations of the magnitude of interaction were included in only 11 papers. Quantitative methodology varied across studies in terms of the null hypothesis, response measured, POD used to test for **synergy**, and consideration of the slope of the dose-response curve. It was concluded that consistent approaches should be applied for quantification of **synergy**, including that **synergy** be defined in terms of departure from dose additivity; uniform procedures be developed for assessing **synergy** at low exposures; and the method for determining the POD for calculating **synergy** be standardized. After evaluation of the six studies that provided useful quantitative estimates of **synergy**, the magnitude of **synergy** at low doses did not exceed the levels predicted by additive models by more than a factor of 4.”

http://www.ncbi.nlm.nih.gov/pubmed/21309635

European Journal Of Pharmacology • June 2011

Luteolin and chicoric acid synergistically inhibited inflammatory responses via inactivation of PI3K-Akt pathway and impairment of NF-ßB translocation in LPS stimulated RAW 264.7 cells

Author information

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Abstract

Synergistic anti-inflammatory effects of luteolin and chicoric acid, two abundant constituents of the common dandelion (Taraxacum officinale Weber), were investigated in lipopolysaccharide (LPS) stimulated RAW 264.7 cells. Co-treatment with luteolin and chicoric acid synergistically reduced cellular concentrations of nitric oxide (NO) and prostaglandin E2 (PGE2) and also inhibited expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). In addition, co-treatment reduced the levels of pro-inflammatory cytokines, tumor necrosis factor (TNF)-ß, and interleukin (IL)-1ß. Both luteolin and chicoric acid suppressed oxidative stress, but they did not exhibit any synergistic activity. Luteolin and chicoric acid co-treatment inhibited phosphorylation of NF-ßB and Akt, but had no effect on extracellular signal-regulated kinase (ERK), c-Jun NH2-terminal kinase (JNK), and p38. This anti-inflammatory signaling cascade coincides with that affected by luteolin treatment alone. These results suggest that luteolin plays a central role in ameliorating LPS-induced inflammatory cascades via inactivation of the NF-ßB and Akt pathways, and that chicoric acid strengthens the anti-inflammatory activity of luteolin through NF-ßB attenuation.

http://www.ncbi.nlm.nih.gov/pubmed/21513709

“**Synergistic** anti-inflammatory effects of luteolin and chicoric acid, two abundant constituents of the common dandelion (Taraxacum officinale Weber), were investigated in lipopolysaccharide (LPS) stimulated RAW 264.7 cells. These results suggest that luteolin plays a central role in ameliorating LPS-induced inflammatory cascades via inactivation of the NF-ßB and Akt pathways, and that chicoric acid strengthens the anti-inflammatory activity of luteolin through NF-ßB attenuation.”

Archives In Oral Biology • June 2011

In vitro synergism between berberine and miconazole against planktonic and biofilm Candida cultures

Author information

Wei GX1, Xu X, Wu CD.

Abstract

OBJECTIVES

To investigate the antimycotic activity of the plant alkaloid berberine (BBR), alone and in combination with antifungal azoles, against planktonic and biofilm Candida cultures.

DESIGN

The minimum inhibitory concentrations (MICs) of BBR, miconazole (MCZ), and fluconazole (FLC) towards Candida albicans, Candida glabrata, Candida kefyr, Candida krusei, Candida parapsilosis, and Candida tropicalis were determined by a microdilution method. For C. albicans, the synergistic effects of BBR combined with MCZ or FLC were examined in a paper disc agar diffusion assay and checkerboard microdilution assay. The effect of the BBR/MCZ combination was further investigated in a C. albicans biofilm formation model with a dual-chamber flow cell. The effect on metabolic activity of biofilm cells was established using 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT)/menadione.

RESULTS

Berberine inhibited the growth of various Candida species (MICs 0.98-31.25mg/L) in the following order of susceptibility: C. krusei > C. kefyr > C. glabrata > C. tropicalis > C. parapsilosis and C. albicans. Synergism between BBR and MCZ or FLC was observed in the disc diffusion assay as well as in suspension showing an FIC index <0.5 (∑FIC=0.19). Whilst neither BBR (16 mg/L) nor MCZ (0.8 mg/L) alone significantly inhibited biofilm formation of C. albicans, their combination reduced biofilm formation by >91% after 24 h, as established from the reduction in surface area coverage (P<0.01). The BBR/MCZ combination also exhibited synergy against the metabolic activity of pre-formed C. albicans biofilms in polystyrene microtiter plates (∑FIC=0.25).

CONCLUSION

Berberine exhibits synergistic effects with commonly used antimycotic drugs against C. albicans, either in planktonic or in biofilm growth phases.

http://www.ncbi.nlm.nih.gov/pubmed/21272859

CONCLUSION

“Berberine exhibits **synergistic** effects with commonly used antimycotic drugs against C. albicans, either in planktonic or in biofilm growth phases.”

“This observation accounted for the first time for the peculiar phenomenon of **synergy** between some sweeteners.”

Advances In Food And Nutrition Research • July 2007

The sweet taste receptor: a single receptor with multiple sites and modes of interaction

Author information

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Abstract

Elucidation of the molecular bases of sweet taste is very important not only for its intrinsic biological significance but also for the design of new artificial sweeteners. Up to few years ago design was complicated by the common belief that different classes of sweet compounds, notably sweet proteins, might interact with different receptors altogether. The recent identification and functional expression of the receptor for sweet taste have shown that there is but one receptor, drastically changing our approach to the development of new sweeteners. The explanation of how the sweet receptor can bind several different classes of molecules is that rather than multiple receptors there are, apparently, multiple sites on the single sweet taste receptor. In this chapter, the mechanisms of interaction of small and macromolecular sweet molecules will be examined, with particular emphasis on sweet proteins. Systematic homology modeling yields reliable models of all possible heterodimers of the human T1R2 and T1R3 sequences with the closed (A) and open (B) conformations of one of the metabotropic glutamate receptors (mGluR1), used as template. The most important result of these studies is the “wedge model,” the first explanation of the taste of sweet proteins. In addition, it was shown that simultaneous binding to the A and B sites is not possible with two large sweeteners but is possible with a small molecule in site A and a large one in site B. This observation accounted for the first time for the peculiar phenomenon of synergy between some sweeteners.

http://www.ncbi.nlm.nih.gov/pubmed/17900500

“... a human study indicated **synergistic** effects of folic acid (synthetic form of folate) and vitamin B(6) together with omega-3 fatty acids on the atherogenic index and the fibrinogen concentration.”

European Journal Of Clinical Nutrition • May 2004

Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases

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Abstract

The results of dietary intervention trials favor the hypothesis that higher intakes of B-vitamins (folate, vitamin B(6) and B(12)), and subsequently lower total homocysteine (tHcy) concentrations, are causally associated with a decreased risk of vascular disease in patients with cardiovascular diseases (CVD). The same is true for a higher intake of omega-3 fish fatty acids. Yet, the lack of hard end points and/or appropriate study designs precludes a definitive conclusion about causality. In the future, intervention trials with hard end points and randomized double-blind placebo-controlled designs should be able to elucidate the causality problem. There are several pathways by which B-vitamins and omega-3 fatty acids may exert their protective effect on CVD, a common pathway is a beneficial effect on the endothelial function and hemostasis. With respect to synergy between B-vitamins and omega-3 fatty acids, there is no evidence that fish oils have a tHcy-lowering effect beyond the effect of the B-vitamins. Nevertheless, animal studies clearly illustrate that vitamin B(6)- as well as folate-metabolism are linked with those of long-chain omega-3 fatty acids. Furthermore, a human study indicated synergistic effects of folic acid (synthetic form of folate) and vitamin B(6) together with omega-3 fatty acids on the atherogenic index and the fibrinogen concentration. Although these results are promising, they were produced in very small selective study populations. Thus, confirmation in large well-designed intervention trials is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/15116076

“We proposed that the additive and **synergistic** effects of phytochemicals in fruits and vegetables are responsible for these potent antioxidant and anticancer activities and that the benefit of a diet rich in fruits and vegetables is attributed to the complex mixture of phytochemicals present in whole foods. This [**synergy**] explains why no single antioxidant can replace the combination of natural phytochemicals in fruits and vegetables to achieve the health benefits. **The evidence suggests that antioxidants or bioactive compounds are best acquired through whole-food consumption, not from expensive dietary supplements.**”

Journal Of Nutrition • December 2004

Potential synergy of phytochemicals in cancer prevention: mechanism of action

By R.H. Liu

Abstract

Epidemiological studies have consistently shown that regular consumption of fruits and vegetables is strongly associated with reduced risk of developing chronic diseases, such as cancer and cardiovascular disease. It is now widely believed that the actions of the antioxidant nutrients alone do not explain the observed health benefits of diets rich in fruits and vegetables, because taken alone, the individual antioxidants studied in clinical trials do not appear to have consistent preventive effects. Work performed by our group and others has shown that fruits and vegetable phytochemical extracts exhibit strong antioxidant and antiproliferative activities and that the major part of total antioxidant activity is from the combination of phytochemicals. We proposed that the additive and synergistic effects of phytochemicals in fruits and vegetables are responsible for these potent antioxidant and anti-cancer activities and that the benefit of a diet rich in fruits and vegetables is attributed to the complex mixture of phytochemicals present in whole foods. This explains why no single antioxidant can replace the combination of natural phytochemicals in fruits and vegetables to achieve the health benefits. The evidence suggests that antioxidants or bioactive compounds are best acquired through whole-food consumption, not from expensive dietary supplements. We believe that a recommendation that consumers eat 5 to 10 servings of a wide variety of fruits and vegetables daily is an appropriate strategy for significantly reducing the risk of chronic diseases and to meet their nutrient requirements for optimum health.

Full text, graphs, charts and 40 references

http://jn.nutrition.org/content/134/12/3479S.long

“We propose that the additive and **synergistic** effects of phytochemicals in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods.”

The American Journal Of Clinical Nutrition • January 2003

Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals

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Abstract

Cardiovascular disease and cancer are ranked as the first and second leading causes of death in the United States and in most industrialized countries. Regular consumption of fruit and vegetables is associated with reduced risks of cancer, cardiovascular disease, stroke, Alzheimer disease, cataracts, and some of the functional declines associated with aging. Prevention is a more effective strategy than is treatment of chronic diseases. Functional foods that contain significant amounts of bioactive components may provide desirable health benefits beyond basic nutrition and play important roles in the prevention of chronic diseases. The key question is whether a purified phytochemical has the same health benefit as does the whole food or mixture of foods in which the phytochemical is present. Our group found, for example, that the vitamin C in apples with skin accounts for only 0.4% of the total antioxidant activity, suggesting that most of the antioxidant activity of fruit and vegetables may come from phenolics and flavonoids in apples. We propose that the additive and synergistic effects of phytochemicals in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods.

Full text, graphs, charts and 35 references

http://ajcn.nutrition.org/content/78/3/517S.full.pdf

“As part of this pilot study we also investigated whether specific fruits and vegetables are responsible for the anticancer action of these foods or whether a wide variety is required for optimal protection. If the former is correct, then fruits and vegetables may contain one or a small number of “magic bullets”; if the latter is correct, then a “teamwork” [or **synergy**] concept may be valid.”

Nutrition • May 2003

Fruit, vegetables, and the prevention of cancer: research challenges

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Abstract

OBJECTIVE
A great deal of epidemiologic evidence has indicated that fruits and vegetables are protective against numerous forms of cancer. However, there are many gaps in our knowledge.
METHODS
In this pilot study we reviewed more than 200 cohort and case-control studies to determine the shape of the dose-response relationship (i.e., how the risk reduction per extra serving of fruits and vegetables changes with the actual intake of these foods). We found major barriers to investigating this. As part of this pilot study we also investigated whether specific fruits and vegetables are responsible for the anticancer action of these foods or whether a wide variety is required for optimal protection. If the former is correct, then fruits and vegetables may contain one or a small number of “magic bullets”; if the latter is correct, then a “teamwork” concept may be valid.
RESULTS
Different findings suggested that the teamwork concept is much more likely. Many studies, especially older ones, have ignored potential confounding variables such as energy intake, alcohol consumption, physical activity, body mass index, smoking, and socioeconomic status (although many recent studies have adjusted for education). Other potential confounders that have generally been ignored are consumption of whole grain cereals and the use of vitamin and mineral supplements.
CONCLUSIONS
The inverse association between intake of fruits and vegetables and the risk of cancer of the colon, breast, and stomach has generally been much stronger in case-control than in cohort studies. We have no clear explanation for this.

http://www.ncbi.nlm.nih.gov/pubmed/12714102?dopt=Abstract

CHAPTER EIGHTEEN

Nitrate & Nitrite

The Peer Review

If you eat cured meats, you've probably encountered sodium nitrate or sodium nitrite. Sodium nitrate is a salt that is often added to jerky, bacon and luncheon meats. Sodium nitrite, on the other hand, is a salt and antioxidant that is commonly used to cure ham and bacon. Both chemicals act as food preservatives and add a red or pink color to processed meats, among other uses. However, MayoClinic.com also associates them with some health concerns.

Sodium Nitrate

Cured meats are not the only sources of sodium nitrate. According to Meatsafety.org, it also occurs in some vegetables and converts into sodium nitrite whenever it comes into contact with your saliva. This conversion may also occur when sodium-containing vegetables are exposed to certain types of bacteria. According to cardiologist Dr. Martha Grogan, sodium nitrate can increase your risk of developing heart disease by damaging your blood vessels. Sodium nitrate may also raise your diabetes risk, says Grogan. Nitrates found in fruits and vegetables may be beneficial in the human diet while industrial nitrates may not be.

Sodium Nitrite

Sodium nitrite is currently used in the medical treatment of cyanide poisoning and has public health use as a curing agent. Indeed, according to Meatsafety.org, sodium nitrite works with sodium chloride, or salt, to inhibit the growth of Clostridium botulinum. Clostridium botulinum is an organism that can cause fatal food poisoning. sodium nitrite is also effective against Listeria monocytogenes, another disease-causing organism. According to the National Institutes of Health, sodium nitrite also shows promise in the treatment of high blood pressure, kidney failure, heart disease and organ damage.

Sodium Nitrate vs. Sodium Nitrite Effects

In oxygen-poor tissues, nitrite can convert into nitric oxide (NO), state the National Institutes of Health. Nitric oxide is a chemical that dilates your blood vessels to enhance blood flow. The protective effect of sodium nitrite might therefore result from its conversion into nitric oxide. Nitrate, on the other hand, cannot convert into nitric oxide in your blood. Even though sodium nitrate can theoretically convert into sodium nitrite, NIH study findings indicate that only low concentrations of nitrite protect the body against tissue injury.

Important Considerations

Meats naturally contain amines, a class of compounds that readily react with nitrite to form nitrosamines. Nitrosamines can cause cancer in humans, says Linus Pauling Institute professor Richard A. Scanlan, Ph.D. The public dilemma has been that sodium nitrite cannot be completely banned, because of its role in preventing botulism. Research and regulations have therefore led to lower amounts in processed meats. However, you should limit your consumption of processed meats in order to reduce nitrosamines in your diet. Instead, opt for lean and fresh meats and add green, leafy vegetables to increase NO intake.

“This review discusses the role of muscle contractile dysfunction in the exercise intolerance characteristic of Heart Failure, and the evidence that dietary NO3 - supplementation may represent a novel and simple therapy for this currently under-appreciated problem.”

Current Heart Failure Reports • June 2016

Dietary Nitrate and Skeletal Muscle Contractile Function in Heart Failure

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Abstract

Heart failure (HF) patients suffer from exercise intolerance that diminishes their ability to perform normal activities of daily living and hence compromises their quality of life. This is due largely to detrimental changes in skeletal muscle mass, structure, metabolism, and function. This includes an impairment of muscle contractile performance, i.e., a decline in the maximal force, speed, and power of muscle shortening. Although numerous mechanisms underlie this reduction in contractility, one contributing factor may be a decrease in nitric oxide (NO) bioavailability. Consistent with this, recent data demonstrate that acute ingestion of NO3 --rich beetroot juice, a source of NO via the NO synthase-independent enterosalivary pathway, markedly increases maximal muscle speed and power in HF patients. This review discusses the role of muscle contractile dysfunction in the exercise intolerance characteristic of HF, and the evidence that dietary NO3 - supplementation may represent a novel and simple therapy for this currently underappreciated problem.

http://www.ncbi.nlm.nih.gov/pubmed/27271563

“In patients with stable COPD, the acute consumption of dietary nitrate increased serum nitrate/nitrite levels and exercise capacity and was associated with a decrease in resting blood pressure.”

Nitric Oxide • January 2015

Dietary nitrate supplementation in COPD: an acute, double-blind, randomized, placebo-controlled, crossover trial

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Abstract

BACKGROUND

The acute consumption of dietary nitrate has been shown to improve exercise capacity in athletes, healthy adults and subjects with peripheral vascular disease. Many COPD patients have reduced exercise capacity. We hypothesized that acute nitrate consumption might increase incremental shuttle walk test (ISWT) distance in COPD subjects.

METHODS

Eleven COPD subjects were randomly assigned to consume either a high nitrate or a matched, low nitrate beverage in a double-blind, randomized, placebo-controlled, crossover design. ISWT distance was measured both before and 3 h after the beverage and change was recorded. After a 7-day washout, ISWT distances were re-measured before and 3 h after the alternate beverage and changes were recorded.

RESULTS

We observed an increase in ISWT distance after consuming the high nitrate juice (25 m) compared with a reduction after the low nitrate juice (14 m) ($p<0.01$). This improvement in exercise capacity was associated with significant increases in serum nitrate ($p<0.000005$) and nitrite ($p<0.01$) levels and a significant lowering of resting blood pressure (<0.05).

CONCLUSIONS

In patients with stable COPD, the acute consumption of dietary nitrate increased serum nitrate/nitrite levels and exercise capacity and was associated with a decrease in resting blood pressure. Nitrate consumption might alter exercise capacity in COPD patients.

http://www.ncbi.nlm.nih.gov/pubmed/25534960

“Nitrate is a natural constituent of the human diet and an approved food additive. It can be partially converted to nitrogen monoxide, which induces vasodilation and thereby decreases blood pressure. This effect is associated with a reduced risk regarding cardiovascular disease, myocardial infarction, and stroke. Moreover, dietary nitrate has been associated with beneficial effects in patients with gastric ulcer, renal failure, or metabolic syndrome. Recent studies indicate that such beneficial health effects due to dietary nitrate may be achievable at intake levels resulting from the daily consumption of nitrate-rich vegetables.”

Molecular Nutrition And Food Research • January 2015

Nitrate and nitrite in the diet: how to assess their benefit and risk for human health

Author information

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Abstract

Nitrate is a natural constituent of the human diet and an approved food additive. It can be partially converted to nitrogen monoxide, which induces vasodilation and thereby decreases blood pressure. This effect is associated with a reduced risk regarding cardiovascular disease, myocardial infarction, and stroke. Moreover, dietary nitrate has been associated with beneficial effects in patients with gastric ulcer, renal failure, or metabolic syndrome. Recent studies indicate that such beneficial health effects due to dietary nitrate may be achievable at intake levels resulting from the daily consumption of nitrate-rich vegetables. N-nitroso compounds are endogenously formed in humans. However, their relevance for human health has not been adequately explored up to now. Nitrate and nitrite are per se not carcinogenic, but under conditions that result in endogenous nitrosation, it cannot be excluded that ingested nitrate and nitrite may lead to an increased cancer risk and may probably be carcinogenic to humans. In this review, the known beneficial and detrimental health effects related to dietary nitrate/nitrite intake are described and the identified gaps in knowledge as well as the research needs required to perform a reliable benefit/risk assessment in terms of long-term human health consequences due to dietary nitrate/nitrite intake are presented.

http://www.ncbi.nlm.nih.gov/pubmed/25164923

“Our results suggest that sodium nitrite improves motor function in old mice, in part by reducing low-grade inflammation in muscle.”

Journal Of Applied Physiology • January 2015

Sodium nitrite supplementation improves motor function and skeletal muscle inflammatory profile in old male mice

Author information

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Abstract

Aging is associated with motor declines that lead to functional limitations and disability, necessitating the development of therapies to slow or reverse these events. We tested the hypothesis that sodium nitrite supplementation attenuates declines in motor function in older C57BL/6 mice. Motor function was assessed using a battery of tests (grip strength, open-field distance, rota-rod endurance) in old animals (age 20-24 mo) at baseline and after 8 wk of sodium nitrite (old nitrite, n = 22, 50 mg/liter) or no treatment (old control, n = 40), and in young reference animals (3 mo, n = 87). Eight weeks of sodium nitrite supplementation improved grip strength (old nitrite, +12.0 ± 14.9% vs. old control, +1.5 ± 15.2%, P < 0.05) and open field distance (old nitrite, +9.5 ± 7.7%, P < 0.01 vs. old control, -28.1 ± 2.0%) and completely restored rota-rod endurance-run time (old nitrite, +3.2 ± 7.1%, P < 0.01 vs. old control, -21.5 ± 7.2%; old nitrite after treatment P > 0.05 vs. young reference). Inflammatory cytokines were markedly increased in quadriceps of old compared with young reference animals (by ELISA, interleukin-1ß [IL-1ß] 3.86 ± 2.34 vs. 1.11 ± 0.74, P < 0.05; interferon-gamma [INF-y] 8.31 ± 1.59 vs. 3.99 ± 2.59, P < 0.01; tumor necrosis factor-alpha [TNF-a] 1.69 ± 0.44 vs. 0.76 ± 0.30 pg/ml, P < 0.01), but were reduced to young reference levels after treatment (old nitrite, IL-1ß 0.67 ± 0.95; INF-y 5.22 ± 2.01, TNF-a 1.21 ± 0.39 pg/ml, P < 0.05 vs. old control, P > 0.05 vs. young reference). Cytokine expression and treatment (old nitrite vs. old control) predicted strength (R(2) = 0.822, P < 0.001, IL-1ß, INF-y, group), open field distance (R(2) = 0.574, P < 0.01, IL-1ß, group) and endurance run time (R(2) = 0.477, P < 0.05, INF-y). Our results suggest that sodium nitrite improves motor function in old mice, in part by reducing low-grade inflammation in muscle.

Full text, graphs, charts and 61 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4297777/

Pediatric Research • January 2015

Dietary intake and bio-activation of nitrite and nitrate in newborn infants

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Abstract

Nitrate and nitrite are commonly thought of as inert end products of nitric oxide (NO) oxidation, possibly carcinogenic food additives, or well-water contaminants. However, recent studies have shown that nitrate and nitrite play an important role in cardiovascular and gastrointestinal homeostasis through conversion back into NO via a physiological system involving enterosalivary recirculation, bacterial nitrate reductases, and enzyme-catalyzed or acidic reduction of nitrite to NO. The diet is a key source of nitrate in adults; however, infants ingest significantly less nitrate due to low concentrations in breast milk. In the mouth, bacteria convert nitrate to nitrite, which has gastro-protective effects. However, these nitrate-reducing bacteria are relatively inactive in infants. Swallowed nitrite is reduced to NO by acid in the stomach, affecting gastric blood flow, mucus production, and the gastric microbiota. These effects are likely attenuated in the less acidic neonatal stomach. Systemically, nitrite acts as a reservoir of NO bioactivity that can protect against ischemic injury, yet plasma nitrite concentrations are markedly lower in infants than in adults. The physiological importance of the diminished nitrate-nitrite-NO axis in infants and its implications in the etiology and treatment of newborn diseases such as necrotizing enterocolitis and hypoxic/ischemic injury are yet to be determined.

Full text, graphs, charts and 87 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4497514/

“The exposure estimate was significantly reduced when using occurrence data, but in the upper-bound scenario the ADI was still exceeded significantly by the age group 13-36 months for benzoates (2%) and BHA (1%), and by the age group 7-12 months (16%) and 13-36 months (58%) for nitrites.”

Food Additives And Contamination • Part A • Chemistry, Analysis, Control, Exposure And Risk Assessment • February 2015

Dietary exposure to benzoates (E210-E213), parabens (E214-E219), nitrites (E249-E250), nitrates (E251-E252), BHA (E320), BHT (E321) and aspartame (E951) in children less than 3 years old in France

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Abstract

This study aimed to estimate the exposure to seven additives (benzoates, parabens, nitrites, nitrates, BHA, BHT and aspartame) in children aged less than 3 years old in France. A conservative approach, combining individual consumption data with maximum permitted levels, was carried out for all the additives. More refined estimates using occurrence data obtained from products' labels (collected by the French Observatory of Food Quality) were conducted for those additives that exceeded the acceptable daily intake (ADI). Information on additives' occurrence was obtained from the food labels. When the ADI was still exceeded, the exposure estimate was further refined using measured concentration data, if available. When using the maximum permitted level (MPL), the ADI was exceeded for benzoates (1.94 mg kg(-1) bw day(-1)), nitrites (0.09 mg kg(-1) bw day(-1)) and BHA (0.39 mg kg(-1) bw day(-1)) in 25%, 54% and 20% of the entire study population respectively. The main food contributors identified with this approach were current foods as these additives are not authorised in specific infant food: vegetable soups and broths for both benzoates and BHA, delicatessen and meat for nitrites. The exposure estimate was significantly reduced when using occurrence data, but in the upper-bound scenario the ADI was still exceeded significantly by the age group 13-36 months for benzoates (2%) and BHA (1%), and by the age group 7-12 months (16%) and 13-36 months (58%) for nitrites. Measured concentration data were available exclusively for nitrites and the results obtained using these data showed that the nitrites' intake was below the ADI for all the population considered in this study. These results suggest that refinement of exposure, based on the assessment of food levels, is needed to estimate the exposure of children to BHA and benzoates for which the risk of exceeding the ADI cannot be excluded when using occurrence data.

http://www.ncbi.nlm.nih.gov/pubmed/25686474

“Because resulting beige/brite cells exhibit antiobesity and antidiabetic effects, nitrate may be an effective means of inducing the browning response in adipose tissue to treat the metabolic syndrome.”

Diabetes • February 2015

Inorganic nitrate promotes the browning of white adipose tissue through the nitrate-nitrite-nitric oxide pathway

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Abstract

Inorganic nitrate was once considered an oxidation end product of nitric oxide metabolism with little biological activity. However, recent studies have demonstrated that dietary nitrate can modulate mitochondrial function in man and is effective in reversing features of the metabolic syndrome in mice. Using a combined histological, metabolomics, and transcriptional and protein analysis approach, we mechanistically defined that nitrate not only increases the expression of thermogenic genes in brown adipose tissue but also induces the expression of brown adipocyte-specific genes and proteins in white adipose tissue, substantially increasing oxygen consumption and fatty acid ß-oxidation in adipocytes. Nitrate induces these phenotypic changes through a mechanism distinct from known physiological small molecule activators of browning, the recently identified nitrate-nitrite-nitric oxide pathway. The nitrate-induced browning effect was enhanced in hypoxia, a serious comorbidity affecting white adipose tissue in obese individuals, and corrected impaired brown adipocyte-specific gene expression in white adipose tissue in a murine model of obesity. Because resulting beige/brite cells exhibit antiobesity and antidiabetic effects, nitrate may be an effective means of inducing the browning response in adipose tissue to treat the metabolic syndrome.

Full text, graphs, charts and 48 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4351918/

“We suggest that the bacterial nitrate reduction to ammonia, as well as the related NO formation in the gut, could be an important aspect of the overall mammalian nitrate/nitrite/NO metabolism and is yet another way in which the microbiome links diet and health.”

PLoS One • March 2015

Nitrate reduction to nitrite, nitric oxide and ammonia by gut bacteria under physiological conditions

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Abstract

The biological nitrogen cycle involves step-wise reduction of nitrogen oxides to ammonium salts and oxidation of ammonia back to nitrites and nitrates by plants and bacteria. Neither process has been thought to have relevance to mammalian physiology; however in recent years the salivary bacterial reduction of nitrate to nitrite has been recognized as an important metabolic conversion in humans. Several enteric bacteria have also shown the ability of catalytic reduction of nitrate to ammonia via nitrite during dissimilatory respiration; however, the importance of this pathway in bacterial species colonizing the human intestine has been little studied. We measured nitrite, nitric oxide (NO) and ammonia formation in cultures of Escherichia coli, Lactobacillus and Bifidobacterium species grown at different sodium nitrate concentrations and oxygen levels. We found that the presence of 5 mM nitrate provided a growth benefit and induced both nitrite and ammonia generation in E.coli and L.plantarum bacteria grown at oxygen concentrations compatible with the content in the gastrointestinal tract. Nitrite and ammonia accumulated in the growth medium when at least 2.5 mM nitrate was present. Time-course curves suggest that nitrate is first converted to nitrite and subsequently to ammonia. Strains of L.rhamnosus, L.acidophilus and B.longum infantis grown with nitrate produced minor changes in nitrite or ammonia levels in the cultures. However, when supplied with exogenous nitrite, NO gas was readily produced independently of added nitrate. Bacterial production of lactic acid causes medium acidification that in turn generates NO by non-enzymatic nitrite reduction. In contrast, nitrite was converted to NO by E.coli cultures even at neutral pH. We suggest that the bacterial nitrate reduction to ammonia, as well as the related NO formation in the gut, could be an important aspect of the overall mammalian nitrate/nitrite/NO metabolism and is yet another way in which the microbiome links diet and health.

Full text, graphs, charts and 57 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4372352/

“The presence of nitrite in food is free of danger and a diet high in nitrate is beneficial to the health.”

Journal Of Ethnopharmacology • June 2015

Nitrites and nitrates in the human diet: Carcinogens or beneficial hypotensive agents?

Author information

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Abstract

ETHNOPHARMACOLOGICAL RELEVANCE
The presence of nitrite in the human diet was thought to constitute a hazard as secondary nitrosamines are known to cause gastric cancers.
MATERIALS AND METHODS
Recent publications on the physiology of serum nitrite have been consulted.
PROBLEMS
Nitrite is added to some foodstuffs as an antibotulinum agent.
RESULTS AND DISCUSSION
The epidemiological evidence that nitrite causes gastric ulcers is weak. On the other hand, evidence that the presence of nitrite in serum lowers blood pressure is strong. This allows us to explain why a Tang dynasty treatment for angina, given in a Dunhuang medical manuscript, can be successful.
CONCLUSION
The presence of nitrite in food is free of danger and a diet high in nitrate is beneficial to the health.

http://www.ncbi.nlm.nih.gov/pubmed/25300670

“Recently accumulated evidence has demonstrated that dietary intake of fruits and vegetables rich in nitrate/nitrite is an inexpensive and easily-practicable way to prevent insulin resistance and vascular endothelial dysfunction by increasing the NO availability; a NO-rich diet may also prevent other lifestyle-related diseases, including osteoporosis, chronic obstructive pulmonary disease (COPD), and cancer.”

Nutrients • June 2015

NO-Rich Diet for Lifestyle-Related Diseases

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Abstract

Decreased nitric oxide (NO) availability due to obesity and endothelial dysfunction might be causally related to the development of lifestyle-related diseases such as insulin resistance, ischemic heart disease, and hypertension. In such situations, instead of impaired NO synthase (NOS)-dependent NO generation, the entero-salivary nitrate-nitrite-NO pathway might serve as a backup system for NO generation by transmitting NO activities in the various molecular forms including NO and protein S-nitrosothiols. Recently accumulated evidence has demonstrated that dietary intake of fruits and vegetables rich in nitrate/nitrite is an inexpensive and easily-practicable way to prevent insulin resistance and vascular endothelial dysfunction by increasing the NO availability; a NO-rich diet may also prevent other lifestyle-related diseases, including osteoporosis, chronic obstructive pulmonary disease (COPD), and cancer. This review provides an overview of our current knowledge of NO generation through the entero-salivary pathway and discusses its safety and preventive effects on lifestyle-related diseases.

Full text, graphs, charts and 166 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4488823/

“This review highlights the anti-inflammatory roles of nitrite in numerous clinical conditions, including ischemia/reperfusion, transplant, cardiac arrest, and vascular injury, and in gastrointestinal inflammation.”

Antioxidants And Redox Signaling • August 2015

Nitrate/Nitrite as Critical Mediators to Limit Oxidative Injury and Inflammation

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Abstract

SIGNIFICANCE

Nitric oxide (NO) is a critical signaling molecule marked by complex chemistry and varied biological responses depending on the context of the redox environment. In the setting of inflammation, NO can not only contribute to tissue injury and be causative of oxidative damage but can also signal as an adaptive molecule to limit inflammatory signaling in multiple cell types and tissues.

RECENT ADVANCES

An advance in our understanding of NO biology was the recognition of the nitrate-nitrite-NO axis, whereby nitrate (predominantly from dietary sources) could be converted to nitrite and nitrite could be reduced to NO.

CRITICAL ISSUES

Intriguingly, the recognition of multiple enzymes that serve as nitrite reductases in the setting of hypoxia or ischemia established the concept of nitrite as a circulating endocrine reservoir of NO, with the selective release of NO at sites that were primed for this reaction. This review highlights the anti-inflammatory roles of nitrite in numerous clinical conditions, including ischemia/reperfusion, transplant, cardiac arrest, and vascular injury, and in gastrointestinal inflammation.

FUTURE DIRECTIONS

These preclinical and clinical investigations set up further clinical trials and studies that elucidate the endogenous role this pathway plays in protection against inflammatory signaling.

http://www.ncbi.nlm.nih.gov/pubmed/26140517

“These results indicate that acute dietary NO3(-) supplementation can elevate plasma NO3(-) and NO2(-) concentrations, improve exercise performance, and reduce blood pressure in COPD patients.”

Nitric Oxide • August 2015

Dietary nitrate supplementation improves exercise performance and decreases blood pressure in COPD patients

Author information

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Abstract

Dietary nitrate (NO3(-)) supplementation via beetroot juice has been shown to increase the exercise capacity of younger and older adults. The purpose of this study was to investigate the effects of acute NO3(-) ingestion on the submaximal constant work rate exercise capacity of COPD patients. Fifteen patients were assigned in a randomized, single-blind, crossover design to receive one of two treatments (beetroot juice then placebo or placebo then beetroot juice). Submaximal constant work rate exercise time at 75% of the patient’s maximal work capacity was the primary outcome. Secondary outcomes included plasma NO3(-) and nitrite (NO2(-)) levels, blood pressure, heart rate, oxygen consumption (VO2), dynamic hyper-inflation, dyspnea and leg discomfort. Relative to placebo, beetroot ingestion increased plasma NO3(-) by 938% and NO2(-) by 379%. Median (+interquartile range) exercise time was significantly longer ($p = 0.031$) following the ingestion of beetroot versus placebo (375.0 + 257.0 vs. 346.2 + 148.0 s, respectively). Compared with placebo, beetroot ingestion significantly reduced iso-time ($p = 0.001$) and end exercise ($p = 0.008$) diastolic blood pressures by 6.4 and 5.6 mmHg, respectively. Resting systolic blood pressure was significantly reduced ($p = 0.019$) by 8.2 mmHg for the beetroot versus the placebo trial. No other variables were significantly different between the beetroot and placebo trials. These results indicate that acute dietary NO3(-) supplementation can elevate plasma NO3(-) and NO2(-) concentrations, improve exercise performance, and reduce blood pressure in COPD patients.

http://www.ncbi.nlm.nih.gov/pubmed/25445634

> “In this pilot study, acute dietary nitric oxide3 (-) intake was well tolerated and enhanced nitric oxide bioavailability and muscle power in patients with systolic heart failure.”

Circulation, Heart Failure • September 2015

Acute Dietary Nitrate Intake Improves Muscle Contractile Function in Patients With Heart Failure: A Double-Blind, Placebo-Controlled, Randomized Trial

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Abstract

BACKGROUND

Skeletal muscle strength, velocity, and power are markedly reduced in patients with heart failure, which contributes to their impaired exercise capacity and lower quality of life. This muscle dysfunction may be partially because of decreased nitric oxide (NO) bioavailability. We therefore sought to determine whether ingestion of inorganic nitrate (NO3 (-)) would increase NO production and improve muscle function in patients with heart failure because of systolic dysfunction.

METHODS AND RESULTS

Using a double-blind, placebo-controlled, randomized crossover design, we determined the effects of dietary NO3 (-) in 9 patients with heart failure. After fasting overnight, subjects drank beetroot juice containing or devoid of 11.2 mmol of NO3 (-). Two hours later, muscle function was assessed using isokinetic dynamometry. Dietary NO3 (-) increased ($P<0.05$-0.001) breath NO by 35% to 50%. This was accompanied by 9% ($P=0.07$) and 11% ($P<0.05$) increases in peak knee extensor power at the 2 highest movement velocities tested (ie, 4.71 and 6.28 rad/s). Maximal power (calculated by fitting peak power data with a parabola) was therefore greater (ie, 4.74±0.41 versus 4.20±0.33 W/kg; $P<0.05$) after dietary NO3 (-) intake. Calculated maximal velocity of knee extension was also higher after NO3 (-) ingestion (ie, 12.48±0.95 versus 11.11±0.53 rad/s; $P<0.05$). Blood pressure was unchanged, and no adverse clinical events occurred.

CONCLUSIONS

In this pilot study, acute dietary NO3 (-) intake was well tolerated and enhanced NO bioavailability and muscle power in patients with systolic heart failure. Larger-scale studies should be conducted to determine whether the latter translates into an improved quality of life in this population.

http://www.ncbi.nlm.nih.gov/pubmed/26179185

“These results show that sodium nitrite-induced oxidative stress causes hemoglobin denaturation and aggregation, weakens the cellular antioxidant defense mechanism, damages the cell membrane and also perturbs normal energy metabolism in erythrocytes. This nitrite-induced damage can reduce erythrocyte life span in the blood.”

Toxicology In Vitro • October 2015

Sodium nitrite-induced oxidative stress causes membrane damage, protein oxidation, lipid peroxidation and alters major metabolic pathways in human erythrocytes

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Abstract

Nitrite salts are present as contaminants in drinking water and in the food and feed chain. In this work, the effect of sodium nitrite (NaNO2) on human erythrocytes was studied under in vitro conditions. Incubation of erythrocytes with 0.1-10.0 mM NaNO2 at 37 °C for 30 min resulted in dose dependent decrease in the levels of reduced glutathione, total sulfhydryl and amino groups. It was accompanied by increase in hemoglobin oxidation and aggregation, lipid peroxidation, protein oxidation and hydrogen peroxide levels suggesting the induction of oxidative stress. Activities of all major erythrocyte antioxidant defense enzymes were decreased in NaNO2-treated erythrocytes. The activities of enzymes of glycolytic and pentose phosphate pathways were also compromised. However, there was a significant increase in acid phosphatase and also AMP deaminase, a marker of erythrocyte oxidative stress. Thus, the major metabolic pathways of cell were altered. Erythrocyte membrane damage was suggested by lowered activities of membrane bound enzymes and confirmed by electron microscopic images. These results show that NaNO2-induced oxidative stress causes hemoglobin denaturation and aggregation, weakens the cellular antioxidant defense mechanism, damages the cell membrane and also perturbs normal energy metabolism in erythrocytes. This nitrite-induced damage can reduce erythrocyte life span in the blood.

http://www.ncbi.nlm.nih.gov/pubmed/26231821

“High nitrates intake was associated with a weak but statistically significant reduced risk of gastric cancer. Whereas increased consumption of nitrites and N-nitrosodimethylamine seemed to be risk factors for cancer.”

Nutrients • December 2015

Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis

Author information

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Abstract

The potential associations between dietary consumption of nitrates, nitrites, and nitrosamines and gastric cancer risk have been investigated by several studies, but yielded inconclusive results. We conducted a meta-analysis to provide a quantitative assessment of their relationships. Relevant articles were identified by a systematic literature searching of PubMed and Embase databases prior to August 2015. Random-effects models were employed to pool the relative risks. A total of 22 articles consisting of 49 studies-19 studies for nitrates, 19 studies for nitrites, and 11 studies for N-nitrosodimethylamine (NDMA)-were included. The summary relative risk of stomach cancer for the highest categories, compared with the lowest, was 0.80 (95% confidence interval (CI), 0.69-0.93) for dietary nitrates intake, 1.31 (95% CI, 1.13-1.52) for nitrites, and 1.34 (95% CI, 1.02-1.76) for NDMA (p for heterogeneity was 0.015, 0.013 and <0.001, respectively). The study type was found as the main source of heterogeneity for nitrates and nitrites. The heterogeneity for NDMA could not be eliminated completely through stratified analysis. Although significant associations were all observed in case-control studies, the cohort studies still showed a slight trend. The dose-response analysis indicated similar results as well. High nitrates intake was associated with a weak but statistically significant reduced risk of gastric cancer. Whereas increased consumption of nitrites and NDMA seemed to be risk factors for cancer. Due to the lack of uniformity for exposure assessment across studies, further prospective researches are warranted to verify these findings.

Full text, graphs, charts and 42 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4690057/

“Domestic intakes of nitrates and nitrites were found to be at safe levels; nevertheless control over their intake should be maintained because of potentially adverse health threats.”

Roczniki Panstwowego Zakladu Higieny • July 2014

Evaluating adult dietary intakes of nitrate and nitrite in Polish households during 2006-2012

Anyzewska A, Wawrzyniak A.

Abstract

INTRODUCTION

Nitrates and nitrites commonly occur throughout nature as well as in foodstuffs. Their excess consumption can however pose health risks, for example, arising from methaemoglobinaemia or from the formation of N-nitrosamines.

OBJECTIVES

To determine whether the levels of domestic nitrate and nitrite consumption are safe in Polish households during 2006-2012.

MATERIAL AND METHODS

Appropriate consumption data was obtained from the Central Statistical Office in Poland (GUS), whilst nitrate and nitrite intakes were estimated from nationally available data on foodstuff content taken from the literature.

RESULTS

Mean nitrate and nitrite intakes were respectively 147 mg NaNO3 and 3.26 mg NaNO2/per person/day, corresponding to 41% and 45% of the ADI (acceptable daily intake). Statistically significant differences in intakes were observed between types of households, with the highest seen in those of retired subjects; however the ADIs were not exceeded.

CONCLUSIONS

Domestic intakes of nitrates and nitrites were found to be at safe levels; nevertheless control over their intake should be maintained because of potentially adverse health threats.

Full text, PDF with 17 references - use link at top right corner of web page

http://www.ncbi.nlm.nih.gov/pubmed/25272576

“These findings suggest that the NO3 (-)-NO2 (-)-NO pathway is a significant modulator of muscle energetics and O2 delivery during hypoxic exercise and subsequent recovery.”

Journal Of Applied Physiology • December 2014

Dietary nitrate accelerates postexercise muscle metabolic recovery and O2 delivery in hypoxia

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Abstract

We tested the hypothesis that the time constants (t) of postexercise T2* MRI signal intensity (an index of O2 delivery) and muscle [PCr] (an index of metabolic perturbation, measured by (31)P-MRS) in hypoxia would be accelerated after dietary nitrate (NO3 (-)) supplementation. In a double-blind crossover design, eight moderately trained subjects underwent 5 days of NO3 (-) (beetroot juice, BR; 8.2 mmol/day NO3 (-)) and placebo (PL; 0.003 mmol/day NO3 (-)) supplementation in four conditions: normoxic PL (N-PL), hypoxic PL (H-PL; 13% O2), normoxic NO3 (-) (N-BR), and hypoxic NO3 (-) (H-BR). The single-leg knee-extension protocol consisted of 10 min of steady-state exercise and 24 s of high-intensity exercise. The [PCr] recovery t was greater in H-PL (30 ± 4 s) than H-BR (22 ± 4 s), N-PL (24 ± 4 s) and N-BR (22 ± 4 s) ($P < 0.05$) and the maximal rate of mitochondrial ATP resynthesis (Qmax) was lower in the H-PL (1.12 ± 0.16 mM/s) compared with H-BR (1.35 ± 0.26 mM/s), N-PL (1.47 ± 0.28 mM/s), and N-BR (1.40 ± 0.21 mM/s) ($P < 0.05$). The t of postexercise T2* signal intensity was greater in H-PL (47 ± 14 s) than H-BR (32 ± 10 s), N-PL (38 ± 9 s), and N-BR (27 ± 6 s) ($P < 0.05$). The postexercise [PCr] and T2* recovery ~ were correlated in hypoxia ($r = 0.60$; $P < 0.05$), but not in normoxia ($r = 0.28$; $P > 0.05$). These findings suggest that the NO3 (-)-NO2 (-)-NO pathway is a significant modulator of muscle energetics and O2 delivery during hypoxic exercise and subsequent recovery.

Full text, graphs, charts and 69 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4269683/

“In order to provide simple guidance on nitrate intake from different vegetables, we have developed the Nitrate ‘Veg-Table’ with ‘Nitrate Units’ [each unit being 1 mmol of nitrate (62 mg)] to achieve a nitrate intake that is likely to be sufficient to derive benefit, but also to minimize the risk of potential side effects from excessive ingestion, given the current available evidence.”

British Journal Of Clinical Pharmacology • March 2013

Vascular effects of dietary nitrate (as found in green leafy vegetables and beetroot) via the nitrate-nitrite-nitric oxide pathway

Author information

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Abstract

The discovery that dietary (inorganic) nitrate has important vascular effects came from the relatively recent realization of the ‘nitrate-nitrite-nitric oxide (NO) pathway’. Dietary nitrate has been demonstrated to have a range of beneficial vascular effects, including reducing blood pressure, inhibiting platelet aggregation, preserving or improving endothelial dysfunction, enhancing exercise performance in healthy individuals and patients with peripheral arterial disease. Pre-clinical studies with nitrate or nitrite also show the potential to protect against ischaemia-reperfusion injury and reduce arterial stiffness, inflammation and intimal thickness. However, there is a need for good evidence for hard endpoints beyond epidemiological studies. Whilst these suggest reduction in cardiovascular risk with diets high in nitrate-rich vegetables (such as a Mediterranean diet), others have suggested possible small positive and negative associations with dietary nitrate and cancer, but these remain unproven. Interactions with other nutrients, such as vitamin C, polyphenols and fatty acids may enhance or inhibit these effects. In order to provide simple guidance on nitrate intake from different vegetables, we have developed the Nitrate ‘Veg-Table’ with ‘Nitrate Units’ [each unit being 1 mmol of nitrate (62 mg)] to achieve a nitrate intake that is likely to be sufficient to derive benefit, but also to minimize the risk of potential side effects from excessive ingestion, given the current available evidence. The lack of data concerning the long term effects of dietary nitrate is a limitation, and this will need to be addressed in future trials.

Full text, graphs, charts and 232 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3575935/

“The results suggest that augmenting the nitrate-nitrite-NO pathway may have important therapeutic applications for improving muscle energetics and functional capacity in hypoxia.”

Journal Of Physiology • November 2011

Dietary nitrate reduces muscle metabolic perturbation and improves exercise tolerance in hypoxia

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Abstract

Exercise in hypoxia is associated with reduced muscle oxidative function and impaired exercise tolerance. We hypothesised that dietary nitrate supplementation (which increases plasma [nitrite] and thus NO bioavailability) would ameliorate the adverse effects of hypoxia on muscle metabolism and oxidative function. In a double-blind, randomised crossover study, nine healthy subjects completed knee-extension exercise to the limit of tolerance (T(lim)), once in normoxia (20.9% O(2); CON) and twice in hypoxia (14.5% O(2)). During 24 h prior to the hypoxia trials, subjects consumed 0.75 L of nitrate-rich beetroot juice (9.3 mmol nitrate; H-BR) or 0.75 L of nitrate-depleted beetroot juice as a placebo (0.006 mmol nitrate; H-PL). Muscle metabolism was assessed using calibrated (31)P-MRS. Plasma [nitrite] was elevated ($P < 0.01$) following BR (194 ± 51 nm) compared to PL (129 ± 23 nm) and CON (142 ± 37 nM). T(lim) was reduced in H-PL compared to CON (393 ± 169 vs. 471 ± 200 s; $P < 0.05$) but was not different between CON and H-BR (477 ± 200 s). The muscle [PCr], [P(i)] and pH changed at a faster rate in H-PL compared to CON and H-BR. The [PCr] recovery time constant was greater ($P < 0.01$) in H-PL (29 ± 5 s) compared to CON (23 ± 5 s) and H-BR (24 ± 5 s). Nitrate supplementation reduced muscle metabolic perturbation during exercise in hypoxia and restored exercise tolerance and oxidative function to values observed in normoxia. The results suggest that augmenting the nitrate-nitrite-NO pathway may have important therapeutic applications for improving muscle energetics and functional capacity in hypoxia.

Full text, graphs, charts and 62 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3240888/

“This risk/benefit balance should be a strong consideration before there are any suggestions for new regulatory or public health guidelines for dietary nitrite and nitrate exposures.”

Nitric Oxide • February 2010

Nutritional epidemiology in the context of nitric oxide biology: a risk-benefit evaluation for dietary nitrite and nitrate

Author information

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Abstract

The discovery of the nitric oxide (NO) pathway in the 1980s represented a critical advance in understanding cardiovascular disease, and today a number of human diseases are characterized by NO insufficiency. In the interim, recent biomedical research has demonstrated that NO can be modulated by the diet independent of its enzymatic synthesis from l-arginine, e.g., the consumption of nitrite- and nitrate-rich foods such as fruits, leafy vegetables, and cured meats along with antioxidants. Regular intake of nitrate-containing food such as green leafy vegetables may ensure that blood and tissue levels of nitrite and NO pools are maintained at a level sufficient to compensate for any disturbances in endogenous NO synthesis. However, some in the public perceive that dietary sources of nitrite and nitrate are harmful, and some epidemiological studies reveal a weak association between foods that contain nitrite and nitrate, namely cured and processed meats, and cancer. This paradigm needs revisiting in the face of undisputed health benefits of nitrite- and nitrate-enriched diets. This review will address and interpret the epidemiological data and discuss the risk-benefit evaluation of dietary nitrite and nitrate in the context of nitric oxide biology. The weak and inconclusive data on the cancer risk of nitrite, nitrate and processed meats are far outweighed by the health benefits of restoring NO homeostasis via dietary nitrite and nitrate. This risk/benefit balance should be a strong consideration before there are any suggestions for new regulatory or public health guidelines for dietary nitrite and nitrate exposures.

http://www.ncbi.nlm.nih.gov/pubmed/19748594

“An ordinary nitrate rich diet may positively affect blood pressure. Our findings further support the importance of the role of dietary nitrate on Blood Presssure regulation suggesting one possible explanation of healthy aspects of traditional Japanese food.”

Nitric Oxide • February 2010

Dietary nitrate in Japanese traditional foods lowers diastolic blood pressure in healthy volunteers

Author information

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Abstract

BACKGROUND

Japanese longevity is the highest in the world. This is partly explained by low occurrence of cardiovascular diseases, which in turn is attributed to the Japanese traditional diet (JTD). Recent research demonstrates that nitric oxide (NO), a key regulator of vascular integrity, can be generated from nitrate (NO(3)(-)), abundantly found in vegetables. It can reduce blood pressure (BP) via its serial reduction to nitrite (NO(2)(-)) and to bioactive NO. Interestingly, JTD is extremely rich in nitrate and the daily consumption is higher than in any other known diet.

OBJECTIVE AND DESIGN

In a randomized, cross-over trial we examined the effect of a 10-day period of JTD on blood pressure in 25 healthy volunteers. Traditional Japanese vegetables were encouraged to be consumed and avoided during the control period. Daily nitrate intake was calculated.

RESULTS

Nitrate naturally provided by the JTD was 18.8 mg/kg/bw/day, exceeding the Acceptable Daily Intake by five times (ADI, 3.7 mg/kg/bw). Plasma and salivary levels of nitrate and nitrite were higher at the end of the JTD period. Diastolic BP decreased on average 4.5 mmHg during JTD compared to the control diet (P=0.0066) while systolic BP was not affected. This effect was evident in normotensive subjects and similar to that seen in the recent studies.

CONCLUSIONS

An ordinary nitrate rich diet may positively affect blood pressure. Our findings further support the importance of the role of dietary nitrate on BP regulation suggesting one possible explanation of healthy aspects of traditional Japanese food.

http://www.ncbi.nlm.nih.gov/pubmed/19887114

“Our findings demonstrate dose-dependent decreases in blood pressure and vasoprotection after inorganic nitrate ingestion in the form of either supplementation or by dietary elevation. In addition, our post hoc analyses intimate sex differences in nitrate processing involving the entero-salivary circulation that are likely to be major contributing factors to the lower blood pressures and the vasoprotective phenotype of premenopausal women.”

Hypertension • August 2010

Inorganic nitrate supplementation lowers blood pressure in humans: role for nitrite-derived NO

Author information

Kapil V1, Milsom AB, Okorie M, Maleki-Toyserkani S, Akram F, Rehman F, Arghandawi S, Pearl V, Benjamin N, Loukogeorgakis S, Macallister R, Hobbs AJ, Webb AJ, Ahluwalia A.

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Abstract

Ingestion of dietary (inorganic) nitrate elevates circulating and tissue levels of nitrite via bioconversion in the entero-salivary circulation. In addition, nitrite is a potent vasodilator in humans, an effect thought to underlie the blood pressure-lowering effects of dietary nitrate (in the form of beetroot juice) ingestion. Whether inorganic nitrate underlies these effects and whether the effects of either naturally occurring dietary nitrate or inorganic nitrate supplementation are dose dependent remain uncertain. Using a randomized crossover study design, we show that nitrate supplementation (KNO(3) capsules: 4 versus 12 mmol [n=6] or 24 mmol of KNO(3) (1488 mg of nitrate) versus 24 mmol of KCl [n=20]) or vegetable intake (250 mL of beetroot juice [5.5 mmol nitrate] versus 250 mL of water [n=9]) causes dose-dependent elevation in plasma nitrite concentration and elevation of cGMP concentration with a consequent decrease in blood pressure in healthy volunteers. In addition, post hoc analysis demonstrates a sex difference in sensitivity to nitrate supplementation dependent on resting baseline blood pressure and plasma nitrite concentration, whereby blood pressure is decreased in male volunteers, with higher baseline blood pressure and lower plasma nitrite concentration but not in female volunteers. Our findings demonstrate dose-dependent decreases in blood pressure and vasoprotection after inorganic nitrate ingestion in the form of either supplementation or by dietary elevation. In addition, our post hoc analyses intimate sex differences in nitrate processing involving the entero-salivary circulation that are likely to be major contributing factors to the lower blood pressures and the vasoprotective phenotype of premenopausal women.

http://www.ncbi.nlm.nih.gov/pubmed/20585108

“These findings may have implications for novel nutrition-based preventive and therapeutic strategies against cardiovascular disease and type 2 diabetes.”

Proceedings Of The National Academy of Science USA • October 2010

Dietary inorganic nitrate reverses features of metabolic syndrome in endothelial nitric oxide synthase-deficient mice

Author information

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Abstract

The metabolic syndrome is a clustering of risk factors of metabolic origin that increase the risk for cardiovascular disease and type 2 diabetes. A proposed central event in metabolic syndrome is a decrease in the amount of bioavailable nitric oxide (NO) from endothelial NO synthase (eNOS). Recently, an alternative pathway for NO formation in mammals was described where inorganic nitrate, a supposedly inert NO oxidation product and unwanted dietary constituent, is serially reduced to nitrite and then NO and other bioactive nitrogen oxides. Here we show that several features of metabolic syndrome that develop in eNOS-deficient mice can be reversed by dietary supplementation with sodium nitrate, in amounts similar to those derived from eNOS under normal conditions. In humans, this dose corresponds to a rich intake of vegetables, the dominant dietary nitrate source. Nitrate administration increased tissue and plasma levels of bioactive nitrogen oxides. Moreover, chronic nitrate treatment reduced visceral fat accumulation and circulating levels of triglycerides and reversed the prediabetic phenotype in these animals. In rats, chronic nitrate treatment reduced blood pressure and this effect was also present during NOS inhibition. Our results show that dietary nitrate fuels a nitrate-nitrite-NO pathway that can partly compensate for disturbances in endogenous NO generation from eNOS. These findings may have implications for novel nutrition-based preventive and therapeutic strategies against cardiovascular disease and type 2 diabetes.

Full text, graphs, charts and 41 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2955084/

Free Radical Biology And Medicine • April 2009

Gastroprotective and blood pressure lowering effects of dietary nitrate are abolished by an antiseptic mouthwash

Author information

Petersson J1, Carlström M, Schreiber O, Phillipson M, Christoffersson G, Jägare A, Roos S, Jansson EA, Persson AE, Lundberg JO, Holm L.

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Abstract

“Recently, it has been suggested that the supposedly inert nitrite anion is reduced in vivo to form bioactive nitric oxide with physiological and therapeutic implications in the gastrointestinal and cardiovascular systems. Intake of nitrate-rich food such as vegetables results in increased levels of circulating nitrite in a process suggested to involve nitrate-reducing bacteria in the oral cavity. Here we investigated the importance of the oral microflora and dietary nitrate in regulation of gastric mucosal defense and blood pressure. Rats were treated twice daily with a commercial antiseptic mouthwash while they were given nitrate-supplemented drinking water. The mouthwash greatly reduced the number of nitrate-reducing oral bacteria and as a consequence, nitrate-induced increases in gastric NO and circulating nitrite levels were markedly reduced. With the mouthwash the observed nitrate-induced increase in gastric mucus thickness was attenuated and the gastroprotective effect against an ulcerogenic compound was lost. Furthermore, the decrease in systemic blood pressure seen during nitrate supplementation was now absent. These results suggest that oral symbiotic bacteria modulate gastrointestinal and cardiovascular function via bioactivation of salivary nitrate. Excessive use of antiseptic mouthwashes may attenuate the bioactivity of dietary nitrate.”

http://www.ncbi.nlm.nih.gov/pubmed/19439233

“The strength of the evidence linking the consumption of nitrate- and nitrite-containing plant foods to beneficial health effects supports the consideration of these compounds as nutrients.”

American Journal Of Clinical Nutrition • July 2009

Food sources of nitrates and nitrites: the physiologic context for potential health benefits

Author information

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and The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, TX (NSB)

Abstract

The presence of nitrates and nitrites in food is associated with an increased risk of gastrointestinal cancer and, in infants, methemoglobinemia. Despite the physiologic roles for nitrate and nitrite in vascular and immune function, consideration of food sources of nitrates and nitrites as healthful dietary components has received little attention. Approximately 80% of dietary nitrates are derived from vegetable consumption; sources of nitrites include vegetables, fruit, and processed meats. Nitrites are produced endogenously through the oxidation of nitric oxide and through a reduction of nitrate by commensal bacteria in the mouth and gastrointestinal tract. As such, the dietary provision of nitrates and nitrites from vegetables and fruit may contribute to the blood pressure-lowering effects of the Dietary Approaches to Stop Hypertension (DASH) diet. We quantified nitrate and nitrite concentrations by HPLC in a convenience sample of foods. Incorporating these values into 2 hypothetical dietary patterns that emphasize high-nitrate or low-nitrate vegetable and fruit choices based on the DASH diet, we found that nitrate concentrations in these 2 patterns vary from 174 to 1222 mg. The hypothetical high-nitrate DASH diet pattern exceeds the World Health Organization’s Acceptable Daily Intake for nitrate by 550% for a 60-kg adult. These data call into question the rationale for recommendations to limit nitrate and nitrite consumption from plant foods; a comprehensive reevaluation of the health effects of food sources of nitrates and nitrites is appropriate. The strength of the evidence linking the consumption of nitrate- and nitrite-containing plant foods to beneficial health effects supports the consideration of these compounds as nutrients.

Full text, PDF, graphs, charts and 102 references

http://ajcn.nutrition.org/content/90/1/1.full.pdf

Nature - Chemical Biology • December 2009

Nitrate and nitrite in biology, nutrition and therapeutics

Author information

Lundberg JO1, Gladwin MT, Ahluwalia A, Benjamin N, Bryan NS, Butler A, Cabrales P, Fago A, Feelisch M, Ford PC, Freeman BA, Frenneaux M, Friedman J, Kelm M, Kevil CG, Kim-Shapiro DB, Kozlov AV, Lancaster JR Jr, Lefer DJ, McColl K, McCurry K, Patel RP, Petersson J, Rassaf T, Reutov VP, Richter-Addo GB, Schechter A, Shiva S, Tsuchiya K, van Faassen EE, Webb AJ, Zuckerbraun BS, Zweier JL, Weitzberg E.

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Abstract

Inorganic nitrate and nitrite from endogenous or dietary sources are metabolized in vivo to nitric oxide (NO) and other bioactive nitrogen oxides. The nitrate-nitrite-NO pathway is emerging as an important mediator of blood flow regulation, cell signaling, energetics and tissue responses to hypoxia. The latest advances in our understanding of the biochemistry, physiology and therapeutics of nitrate, nitrite and NO were discussed during a recent 2-day meeting at the Nobel Forum, Karolinska Institutet in Stockholm.

Full text, graphs, charts and 44 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4038383/

Nature Reviews - Drug Discovery • February 2008

The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics

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Abstract

The inorganic anions nitrate (NO3-) and nitrite (NO2-) were previously thought to be inert end products of endogenous nitric oxide (NO) metabolism. However, recent studies show that these supposedly inert anions can be recycled in vivo to form NO, representing an important alternative source of NO to the classical L-arginine-NO-synthase pathway, in particular in hypoxic states.

http://www.ncbi.nlm.nih.gov/pubmed/18167491

American Journal Of Physiology And Gastrointestinal Liver Physiology • May 2007

Dietary nitrate increases gastric mucosal blood flow and mucosal defense

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Abstract

Salivary nitrate from dietary or endogenous sources is reduced to nitrite by oral bacteria. In the acidic stomach, nitrite is further reduced to bioactive nitrogen oxides, including nitric oxide (NO). In this study, we investigated the gastroprotective role of nitrate intake and of luminally applied nitrite against provocation with diclofenac and taurocholate. Mucosal permeability ((51)Cr-EDTA clearance) and gastric mucosal blood flow (laser-Doppler flowmetry) were measured in anesthetized rats, either pretreated with nitrate in the drinking water or given acidified nitrite luminally. Diclofenac was given intravenously and taurocholate luminally to challenge the gastric mucosa. Luminal NO content and nitrite content in the gastric mucus were determined by chemiluminescence. The effect of luminal administration of acidified nitrite on the mucosal blood flow was also investigated in endothelial nitric oxide synthase-deficient mice. Rats pretreated with nitrate or given nitrite luminally had higher gastric mucosal blood flow than controls. Permeability increased more during the provocation in the controls than in the nitrate- and nitrite-treated animals. Dietary nitrate increased luminal NO levels 50 times compared with controls. Nitrate intake also resulted in nitrite accumulation in the loosely adherent mucous layer; after removal of this mucous layer, blood flow was reduced. Nitrite administrated luminally in endothelial nitric oxide synthase-deficient mice increased mucosal blood flow. We conclude that dietary nitrate and direct luminal application of acidified nitrite decrease diclofenac- and taurocholate-induced mucosal damage. The gastroprotective effect likely involves a higher mucosal blood flow caused by nonenzymatic NO production. These data suggest an important physiological role of nitrate in the diet.

Full text, graphs, charts and 52 references

http://ajpgi.physiology.org/content/292/3/G718

Hypertension • October 1988

The discovery of nitric oxide as the endogenous nitrovasodilator

Author information

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Abstract

Endothelium-derived relaxing factor (EDRF) is a labile humoral agent released by vascular endothelium that mediates the relaxation induced by some vasodilators, including acetylcholine and bradykinin. EDRF also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to vascular endothelium. These actions of EDRF are mediated through stimulation of the soluble guanylate cyclase and the consequent elevation of cyclic guanosine 3',5'-monophosphate. EDRF has been identified as nitric oxide (NO). The pharmacology of NO and EDRF is indistinguishable; furthermore, sufficient NO is released from endothelial cells to account for the biological activities of EDRF. Organic nitrates exert their vasodilator activity following conversion to NO in vascular smooth muscle cells. Thus, NO may be considered the endogenous nitrovasodilator. NO is synthesized by vascular endothelium from the terminal guanido nitrogen atom(s) of the amino acid L-arginine. This indicates the existence of an enzymic pathway in which L-arginine is the endogenous precursor for the synthesis of NO. The discovery of the release of NO by vascular endothelial cells, the biosynthetic pathway leading to its generation, and its interaction with other vasoactive substances opens up new avenues for research into the physiology and pathophysiology of the vessel wall.

Full text, PDF, graphs, charts and 86 references

http://hyper.ahajournals.org/content/12/4/365.full.pdf

Journal Of Applied Physiology • October 2009

Dietary nitrate supplementation reduces the O2 cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans

Author information

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Abstract

"Pharmacological sodium nitrate supplementation has been reported to reduce the O2 cost of submaximal exercise in humans. In this study, we hypothesized that dietary supplementation with inorganic nitrate in the form of beetroot juice (BR) would reduce the O2 cost of submaximal exercise and enhance the tolerance to high-intensity exercise. In a double-blind, placebo (PL)-controlled, crossover study, eight men (aged 19-38 yr) consumed 500 ml/day of either BR (containing 11.2 +/- 0.6 mM of nitrate) or blackcurrant cordial (as a PL, with negligible nitrate content) for 6 consecutive days and completed a series of "step" moderate-intensity and severe-intensity exercise tests on the last 3 days. On days 4-6, plasma nitrite concentration was significantly greater following dietary nitrate supplementation compared with PL (BR: 273 +/- 44 vs. PL: 140 +/- 50 nM; P < 0.05), and systolic blood pressure was significantly reduced (BR: 124 +/- 2 vs. PL: 132 +/- 5 mmHg; P < 0.01). During moderate exercise, nitrate supplementation reduced muscle fractional O2 extraction (as estimated using near-infrared spectroscopy). The gain of the increase in pulmonary O2 uptake following the onset of moderate exercise was reduced by 19% in the BR condition (BR: 8.6 +/- 0.7 vs. PL: 10.8 +/- 1.6 ml.min(-1).W(-1); P < 0.05). During severe exercise, the O2 uptake slow component was reduced (BR: 0.57 +/- 0.20 vs. PL: 0.74 +/- 0.24 l/min; P < 0.05), and the time-to-exhaustion was extended (BR: 675 +/- 203 vs. PL: 583 +/- 145 s; P < 0.05). The reduced O2 cost of exercise following increased dietary nitrate intake has important implications for our understanding of the factors that regulate mitochondrial respiration and muscle contractile energetics in humans."

Full text, graphs, charts and 67 references

http://jap.physiology.org/content/107/4/1144.long

CHAPTER NINETEEN

Theobromine

Theobromine is an alkaloid found in chocolate. It has effects similar to caffeine, and is the reason why chocolate is so highly toxic to dogs. In 2010, a company (Theocorp) requested that the FDA grant theobromine GRAS status so it could be added to bread, cereal, sports drinks, and other foods. The FDA raised several important questions, including whether reproductive and developmental effects seen in animals exposed to theobromine would apply to humans.

They also estimated that human consumption could be up to five times higher than the company reported as safe. The company withdrew their GRAS request, but it was later granted GRAS status anyway, and now is used in foods "outside of FDA oversight," as reported by the Environmental Working Group.

The Peer Review

Theobromine is just one example of an enormous loophole in the FDA's voluntary GRAS notification process. The food additive industry is allowed to designate a substance as GRAS without even notifying the agency, relying instead on 'expert panels.' Theocorp's submission triggered important questions from FDA scientists about the additive's safety. Instead of addressing them, the company withdrew the request, and the GRAS designation was made later without FDA approval. In some cases, companies forego FDA's notification process altogether."

On the other hand, Theobromine in very small amounts and found in organic dark chocolate bars most plentifullyl, has some perfectly miraculous effects. Theobromine, along with other phenols, terpenes and plants 'chemicals' are being tested by numerous researchers worldwide for anti-cancer and other positive human effects right now.

Theobromine may fight cancer, have liver healing qualities and shows incredibly promising results against the ravages of Azheimers disease and dementia.

Theobromine may act as a poison to smaller wild animals in much larger quantities than found in a single chocolate bar and wild animals getting into cases of chocolates have died from Theobromine poisoning but you can be certain that they consumed a heck of a lot of chocolate!

“Our results reinforce the harmful effects of the alcohol use on cognitive tasks, and suggest that continued use of high doses of caffeine cause cognitive impairment during withdrawal of the substance.”

Pharmacology, Biochemistry And Behavior • April 2016

Irish coffee:
Effects of alcohol and caffeine on object discrimination in zebrafish

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Abstract

Many studies regarding the effects of drugs investigate the acute and chronic use of alcohol, but only a few address the effects of caffeine and alcohol combined to the performance of the zebrafish in cognitive tasks. The zebrafish is an important model for studying the effects of drugs on learning, because it has large genetic similarities to humans and the non-invasive administration of the substances favors translational bias of research. In this study, we observed the effects of alcohol and caffeine on zebrafish cognition through an object discrimination test. We noticed that animals subjected to acute alcohol dose and those under alcohol or caffeine withdrawal did not show discrimination. When fish were treated with associated alcohol and caffeine, those chronically treated with alcohol and subjected to moderate acute dose of caffeine showed learning of the task. Our results reinforce the harmful effects of the alcohol use on cognitive tasks, and suggest that continued use of high doses of caffeine cause cognitive impairment during withdrawal of the substance. However, the acute use of caffeine appears to reverse the harmful effects of alcohol withdrawal, allowing discriminative performance equivalent to control fish. Finally, we reiterate the use of zebrafish as a model for drug effects screening and search for active compounds that modulate the alcohol and caffeine effects.

http://www.ncbi.nlm.nih.gov/pubmed/26850919

“The data presented here, along with existing cacao-omics resources, will enable targeted functional genetic screening of defense genes likely to play critical functions in cacao’s defense against its pathogens.”

BMC Genomics • May 2016

Theobroma cacao L. pathogenesis-related gene tandem array members show diverse expression dynamics in response to pathogen colonization

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Abstract

BACKGROUND

The pathogenesis-related (PR) group of proteins are operationally defined as polypeptides that increase in concentration in plant tissues upon contact with a pathogen. To date, 17 classes of highly divergent proteins have been described that act through multiple mechanisms of pathogen resistance. Characterizing these families in cacao, an economically important tree crop, and comparing the families to those in other species, is an important step in understanding cacao’s immune response.

RESULTS

Using publically available resources, all members of the 17 recognized pathogenesis-related gene families in the genome of Theobroma cacao were identified and annotated resulting in a set of ~350 members in both published cacao genomes. Approximately 50 % of these genes are organized in tandem arrays scattered throughout the genome. This feature was observed in five additional plant taxa (three dicots and two monocots), suggesting that tandem duplication has played an important role in the evolution of the PR genes in higher plants. Expression profiling captured the dynamics and complexity of PR genes expression at basal levels and after induction by two cacao pathogens (the oomycete, Phytophthora palmivora, and the fungus, Colletotrichum theobromicola), identifying specific genes within families that are more responsive to pathogen challenge. Subsequent qRT-PCR validated the induction of several PR-1, PR-3, PR-4, and PR-10 family members, with greater than 1000 fold induction detected for specific genes.

CONCLUSIONS

We describe candidate genes that are likely to be involved in cacao’s defense against Phytophthora and Colletotrichum infection and could be potentially useful for marker-assisted selection for breeding of disease resistant cacao varieties. The data presented here, along with existing cacao-omics resources, will enable targeted functional genetic screening of defense genes likely to play critical functions in cacao’s defense against its pathogens.

Full text, graphs, charts and 96 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4869279/

“Taken together, the results indicate that the cacao osmotin and its derived peptides, herein studied, are good candidates for developing biotechnological tools aiming to control phytopathogenic fungi.”

Peptides • May 2016

Antimicrobial properties of two novel peptides derived from Theobroma cacao osmotin

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Abstract

The osmotin proteins of several plants display antifungal activity, which can play an important role in plant defense against diseases. Thus, this protein can be useful as a source for biotechnological strategies aiming to combat fungal diseases. In this work, we analyzed the antifungal activity of a cacao osmotin-like protein (TcOsm1) and of two osmotin-derived synthetic peptides with antimicrobial features, differing by five amino acids residues at the N-terminus. Antimicrobial tests showed that TcOsm1 expressed in Escherichia coli inhibits the growth of Moniliophthora perniciosa mycelium and Pichia pastoris X-33 in vitro. The TcOsm1-derived peptides, named Osm-pepA (H-RRLDRGGVWNLNVNPGTTGARVWARTK-NH2), located at R23-K49, and Osm-pepB (H-GGVWNLNVNPGTTGARVWARTK-NH2), located at G28-K49, inhibited growth of yeasts (Saccharomyces cerevisiae S288C and Pichia pastoris X-33) and spore germination of the phytopathogenic fungi Fusarium f. sp. glycines and Colletotrichum gossypi. Osm-pepA was more efficient than Osm-pepB for S. cerevisiae (MIC=40µM and MIC=127µM, respectively), as well as for P. pastoris (MIC=20µM and MIC=127µM, respectively). Furthermore, the peptides presented a biphasic performance, promoting S. cerevisiae growth in doses around 5µM and inhibiting it at higher doses. The structural model for these peptides showed that the five amino acids residues, RRLDR at Osm-pepA N-terminus, significantly affect the tertiary structure, indicating that this structure is important for the peptide antimicrobial potency. This is the first report of development of antimicrobial peptides from T. cacao. Taken together, the results indicate that the cacao osmotin and its derived peptides, herein studied, are good candidates for developing biotechnological tools aiming to control phytopathogenic fungi.

http://www.ncbi.nlm.nih.gov/pubmed/26996966

Anticancer Agents In Medicine & Chemistry • June 2016

Determination of the Antiproliferative Activity of New Theobromine Derivatives and Evaluation of Their In Vitro Hepatotoxic Effects

Author information

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Abstract

A new series of N-substituted 1-benzyltheobromine-8-thioacetamides were designed and synthesized. Their antiproliferative activity against human chronic myelocytic leukemia cell K562, human T-cell leukemia cell SKW-3 and human acute myeloid leukemia HL-60 was evaluated. For the tested compounds a concentrationdependent cytotoxic activity was observed, with 7g outlined as the most active compound within the series. The targed compounds were obtained in yields of 56 to 85% and their structures were elucidated by FTIR, (1)H NMR, (13)C NMR and microanalyses. The compounds purity was proven by elemental analysis and spectral data. In general, the compounds showed low hepatotoxicity on sub-cellular and cellular level. On isolated rat microsomes only 7d showed toxic effect while theobromine, 1-benzyl-theobromine-thioacetic acid (BTTA) and the other new theobromine derivatives were devoid of toxicity. In isolated rat hepatocytes, when compared to theobromine and BTTA, 7f showed lower cytotoxic effects, and 7d exerted higher cytotoxicity. The results indicate 7g as a promising structure for the design of future compounds with low hepatotoxicity and good antiproliferative activity.

http://www.ncbi.nlm.nih.gov/pubmed/26567622

Food Function • April 2015

Catecholaminergic and cholinergic systems of mouse brain are modulated by LMN diet, rich in theobromine, polyphenols and polyunsaturated fatty acids

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Abstract

The possible modulatory effect of the functional LMN diet, rich in theobromine, polyphenols and polyunsaturated fatty acids, on the catecholaminergic and cholinergic neurotransmission, affecting cognition decline during aging has been studied. 129S1/SvlmJ mice were fed for 10, 20, 30 and 40 days with either LMN or control diets. The enzymes involved in catecholaminergic and cholinergic metabolism were determined by both immunohistological and western blot analyses. Noradrenalin, dopamine and other metabolites were quantified by HPLC analysis. Theobromine, present in cocoa, the main LMN diet component, was analysed in parallel using SH-SY5Y and PC12 cell lines. An enhanced modulatory effect on both cholinergic and catecholaminergic transmissions was observed on 20 day fed mice. Similar effect was observed with theobromine, besides its antioxidant capacity inducing SOD-1 and GPx expression. The enhancing effect of the LMN diet and theobromine on the levels of acetylcholine-related enzymes, dopamine and specially noradrenalin confirms the beneficial role of this diet on the "cognitive reserve" and hence a possible reducing effect on cognitive decline underlying aging and Alzheimer's disease.

http://www.ncbi.nlm.nih.gov/pubmed/25756794

Nutrition & Cancer • February 2014

Theobromine, the primary methylxanthine found in Theobroma cacao, prevents malignant glioblastoma proliferation by negatively regulating phosphodiesterase-4, extracellular signal-regulated kinase, Akt/mammalian target of rapamycin kinase, and nuclear factor-kappa B

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Abstract

Theobromine, a caffeine derivative, is the primary methylxanthine produced by Theobroma cacao. We previously showed that methylxanthines, including caffeine and theophylline, have antitumor and antiinflammatory effects, which are in part mediated by their inhibition of phosphodiesterase (PDE). A member of the PDE family, PDE4, is widely expressed in and promotes the growth of glioblastoma, the most common type of brain tumor. The purpose of this study was to determine whether theobromine could exert growth inhibitory effects on U87-MG, a cell line derived from human malignant glioma. We show that theobromine treatment elevates intracellular cAMP levels and increases the activity of p38 mitogen-activated protein kinase and c-Jun N-terminal kinase, whereas it attenuates p44/42 extracellular signal-regulated kinase activity and the Akt/mammalian target of rapamycin kinase and nuclear factor-kappa B signal pathways. It also inhibits cell proliferation. These results suggest that foods and beverages containing cocoa bean extracts, including theobromine, might be extremely effective in preventing human glioblastoma.

http://www.ncbi.nlm.nih.gov/pubmed/24547961

Medscape • March 2014

Caffeine Toxicity

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Chief Editor

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Excerpts

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed stimulant drug in the world. It is present in a variety of forms: medications, coffee, tea, soft drinks, and chocolate. Because caffeine overdoses, intentional or unintentional, are relatively common in the United States, physicians and other medical personnel must be aware of caffeine toxicity to recognize and treat it appropriately.

BACKGROUND

Caffeine (1,3,7-trimethylxanthine; see the image below) is the most widely consumed stimulant drug in the world. It is present in a variety of forms: medications, coffee, tea, soft drinks, and chocolate. About 80% of adults in the United States consume caffeine in the form of coffee or tea on a daily basis. A 2010 study published by the US Food and Drug Administration (FDA) reported the average adult consumes about 300 mg caffeine/day, with teenagers consuming roughly one third of that amount. In quantities found in food and beverages, caffeine is unlikely to cause acute medical problems; however, a changing market in which energy drinks are not subject to FDA regulatory standards raises new concerns over caffeine-related health problems. In 1989, the US Food and Drug Administration (FDA) limited the amount of caffeine in OTC products to a maximum of 200 mg/dose. The ingestion of such concentrated sources of caffeine is the general cause of acute caffeine toxicity. See the first chart at the top of the next page for caffeine equivalents of common products. Caffeine has differing CNS, cardiovascular, and metabolic effects based on the quantity ingested. Average doses of caffeine (85-250

mg, the equivalent of 1-3 cups of coffee) may result in feelings of alertness, decreased fatigue, and eased flow of thought. High doses (250-500 mg) can result in restlessness, nervousness, insomnia, and tremors. In high doses, caffeine can cause a hyperadrenergic syndrome resulting in seizures and cardiovascular instability.

Because caffeine overdoses, intentional or unintentional, are relatively common in the United States, physicians and other medical personnel must be aware of caffeine toxicity to recognize and treat it appropriately. FDA regulation on caffeine depends on whether the product is classified as a food, drug, or dietary supplement. In 1989, the FDA limited the amount of caffeine in over-the-counter products to a maximum of 200 mg/dose. Caffeine is present in concentrated forms in over-the-counter products, such as alertness-promoting medications (eg, NoDoz, Vivarin), menstrual aids (eg, Midol), analgesics (eg, Excedrin, Anacin, BC Powder), and diet aids (eg, Dexatrim). Caffeine is also a component of prescription medications (eg, Fioricet, Cafergot) and herbal preparations.

In cola beverages, caffeine is permitted by the FDA for flavor use at a 0.02% (0.2 mg/mL) concentration, equivalent to 20 mg in a 100-mL beverage or 71 mg in a 12-ounce beverage (Code of Federal Regulations, title 21, sec. 182.1180).[1] Because caffeine is not considered a nutrient, the FDA does not require manufacturers to label the amount of caffeine present in food and beverages, although caffeine must be listed as an ingredient if the manufacturer adds it to their product.[2] Caffeine content, at right, of various foods, beverages, medications, and supplements. Caffeine content is approximate for brewed beverages and chocolate).

Although caffeine is found in food and over-the-counter products, more than 97% of caffeine consumed by adults and teenagers comes from beverages, including coffee, tea, cola-products, and energy drinks.[3] Unlike cola-beverages, energy drinks and shots are typically classified as dietary supplements; thus, individuals who consume these products are likely unaware of how much caffeine they are actually consuming.[2]

The caffeine content of dietary supplements is virtually unregulated by the FDA. Prior to the Dietary Supplement Health and Education Act (DSHEA) of 1994, dietary supplements were subject to the same regulatory requirements as other foods; however, after DSHEA, the safety of dietary supplements became the sole responsibility of manufacturers. Consequentially, there are no limitations on the amount of caffeine in dietary supplements and manufacturers are not required to list the caffeine content of their products.[4] The ingestion of concentrated sources of caffeine is the general cause of acute caffeine toxicity.

The rising popularity of caffeinated energy drinks over the past decade has raised new concerns about their impact on public health.

Milk Chocolate	8 oz	5
Dark Chocolate	1 oz	20
Brewed Green Tea	8 oz	20
Anacin	1 tablet	32
Pepsi Cola	12 oz can	38
Espresso	1 oz shot	40
Fiorinal/Fioricet	1 tablet	40
Coca Cola	12 oz can	46
Brewed Black Tea	8 oz	50
Mountain Dew	12 oz can	54
Midol	1 gelcap	60
Excedrin	1 tablet	65
Dexatrim Natural	1 tablet	80
Jolt Cola	12 oz can	80
Red Bull	8.3 oz can	80
Monster	16 oz can	80
Jolt Caffeine Energy Gum	2 pieces	100
Penguin Caffeine Mints	6 pieces	100
Cafergot	1 tablet	100
No Doz	1 tablet	100
Brewed Coffee	12 oz cup	200
Vivarin	1 tablet	200
Ripped Fuel Extreme	2 capsules	200

Table 1. Reported Caffeine Content of Common Items[3]
In Milligrams

As illustrated above, energy drinks contain substantially more caffeine than conventional cola beverages, with caffeine content ranging from 75-300 mg per serving. Many also contain caffeine-containing ingredients such as guarana, kola nut, or yerba mate. Consequentially, they may contain more caffeine than reported in Table 1 at left, center.[5] These energy drinks are also sold in larger sizes (16-23.5 fl oz). It is not uncommon for individuals to consume multiple caffeinated beverages over the course of a day.

Caffeine has differing Central Nervous System, cardiovascular, and metabolic effects based on the quantity ingested. Average doses of caffeine (85-250 mg, the equivalent of 1-3 cups of coffee) may result in feelings of alertness, decreased fatigue, and eased flow of thought. High doses (250-500 mg) can result in restlessness, nervousness, insomnia, and tremors. In high doses, caffeine can cause a hyperadrenergic syndrome resulting in seizures and cardiovascular instability. Because caffeine overdoses, intentional or unintentional, are relatively common in the United States, physicians and other medical personnel must be aware of caffeine toxicity to recognize and treat it appropriately.

PATHOPHYSIOLOGY

Caffeine, a methylxanthine, is closely related to theophylline. Caffeine is rapidly and completely absorbed from the GI tract; it is detectable in the plasma 5 minutes after ingestion, with peak plasma levels occurring in 30-60 minutes. The volume of distribution in adults is approximately 0.5 L/kg. Caffeine is primarily metabolized by the cytochrome P450 (CYP) oxidase system in the liver. The plasma half-life of caffeine varies considerably from person to person, with an average half-life of 5-8 hours in healthy, nonsmoking adults. Caffeine clearance is accelerated in smokers; clearance is slowed in pregnancy, in liver disease, and in the presence of some CYP inhibitors (eg, cimetidine, quinolones, erythromycin). In addition, the hepatic enzyme system responsible for caffeine metabolism can become saturated at high levels, resulting in a marked increase in serum concentration with small additional doses.

Various mechanisms mediate the effects of caffeine in the human body. Caffeine directly stimulates respiratory and vasomotor centers of the brain and acts as an adenosine antagonist, resulting in peripheral vasodilatation and CNS stimulation. Caffeine is a potent releaser of catecholamines (norepinephrine and, to a lesser extent, epinephrine) that increases cardiac chronotropic and inotropic ac-

tivity, bronchodilation, and peripheral vasodilatation. Caffeine is also a phosphodiesterase inhibitor. However, because extremely high concentrations of caffeine are required to inhibit this enzyme, whether this effect contributes to the clinical effects of caffeine in vivo is unknown.

In addition to its cardiovascular effects, caffeine induces a number of metabolic changes, including hyperglycemia (by stimulating gluconeogenesis and glycogenolysis), increased renal filtration, ketosis, and hypokalemia. Caffeine is a potent stimulator of gastric acid secretion and GI motility. Death from caffeine toxicity is rare, but it has been reported due to dysrhythmias, seizures, and aspiration of emesis. Oral doses of caffeine greater than 10 g can be fatal in adults. The average daily adult intake should generally be less than 500 mg/d.

UNITED STATES

Although caffeine poisoning is a relatively common toxicologic emergency in the United States, the number of incidences has steadily increased in the past decade . The Substance Abuse and Mental Health Services Administration (SAMHSA) reported a jump in the number of emergency department visits involving energy drinks, increasing roughly 10-fold from 2005 (1,128 visits) to 2008 and 2009 (16,053 and 13,114 visits, respectively). More than half of the visits made by patients ages 18-25 years involved the combination of energy drinks with alcohol or other drugs.[6] In 2010, American Association of Poison Control Centers' National Poison Data System (AAPCC-NPDS) added "Energy Drinks" to its annual reports, which included several subcategories, including "Caffeine Containing," "Caffeine Only," "Ethanol and Caffeine Containing." and "Ethanol and Caffeine Only." As of March 2013, the AAPCC Web site had an alert urging the public to use caution with energy drink products. The alert also states there were 3150 energy drink exposures in 2012, though the annual AAPCC-NPDS report for 2012 [at the time this report was written] has yet to be released.[7] Caffeinated alcohol beverages were another public health concern; however, the FDA banned their sales in 2010. In spite of the ban, mixing alcohol with energy drinks is still common practice and popular. As a result, it appears that the number of poisonings due to caffeinated energy drinks is continuing to rise.[5] It is very important for the physician to inquire about co-ingestion of caffeine-containing drinks when obtaining history for possible drug overdose or alcohol poisoning.

MORTALITY • MORBIDITY

Death is an uncommon result of caffeine poisoning. According to the AAPC-NPDS, there was only a single death related to caffeine from 2009-2011. However, a separate report published by the FDA's Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS) cited the number of deaths related to caffeinated energy drinks between 2004 and 2010 at a much higher number. In total, they report 16 deaths related solely to Monster, 5-Hour Energy, and Rockstar.[8] In 2010, the FDA received several reports of possible energy drink related fatalities.[9] On a related note, many manufacturers are now changing the classification of their products from "dietary supplements" to "beverages," which means that companies will no longer have to report potential cases linking their products to injury or death to the FDA.[10]

RACE

Caffeine is the most commonly used drug in the world, and its use is prevalent in essentially all races and ethnic groups throughout the world. No scientific data have demonstrated that the outcomes of caffeine exposure differ on the basis of race.

SEX

No scientific data have demonstrated that the outcomes of caffeine exposure differ on the basis of sex. There is not a recommended daily allowance for caffeine but the American Dietetic Association posits that women of reproductive age should consume no more than 300 mg of caffeine per day.[11]

AGE

Whether or not the effects of caffeine on adults can be generalized to children is unclear; however, studies suggest children are differentially affected by caffeine. One study comparing the effects of caffeine in men and boys found that the same dose of caffeine raised blood pressure in both groups but only decreased heart rate in boys. They also found that boys exhibited increased motor activity and speech rates and decreased reaction time compared with men.[12]

Another study found that an intake of 5 mg/kg body weight leads to elevated blood pressure and lower heart rate, without concomitant changes in energy metabolism in children aged 9-11 years. This amounts to 160 mg caffeine/day in a 10-year-old child weighing 30 kg, which is equivalent to the caffeine content of a single 16-oz Monster or Rockstar energy drink. This is consistent with data from an earlier report by the European Food Safety Authority's (EFSA) Scientific Committee on Food, stating that an intake of 5 mg caffeine/kg body weight is sufficient to increase arousal, irritability, nervousness, and anxiety in children, especially if they do not normally consume caffeine.[13] In 2011, the AAPCC-NPDS reported the greatest number of caffeine poisoning cases were in children younger than 5 years (1055), followed by individuals aged 20 years or older (938), then ages 13-19 years (428) and ages 6-12 years (83). Similar trends are observed for caffeinated energy drinks, with which children younger than 5 years have the highest reported poisonings.

Additional age-related concerns arise from the fact that many energy drinks are marketed toward youth and youth-related activities, such as extreme sports. Students and athletes often drink them to enhance performance. A recent survey of 496 college students found that 51% of those surveyed drank more than 1 energy drink

per month, with the majority of students actually drinking several energy drinks per week. The main impetus was the desire for increased energy and concentration, with the most common complaint being insufficient sleep or a disruption in their regular sleep cycles.[14]

Serum caffeine clearance is greatly decreased during the first 6 months of life. Caffeine doses of 78 mg/kg have caused serious adverse effects in young children.

Table 3. Energy Drink Exposure

Item	No. Exposures (single)	Exposures (5)	Exposures (6-12)	Exposures (12-19)	Exposures (20)
Energy Drinks					
Caffeine containing	548	227	60	141	111
Caffeine only	1062	582	91	128	226
Ethanol and caffeine containing	131	15	5	78	28
Ethanol and caffeine pnly	3	1	0	0	2
Pheylnolamine and caffeine combinations (diet aid)	11	5	1	1	4
Caffeine	2655	1055	83	428	938

This has been a series of excerpts from the original. The full text is available at the link below:

http://emedicine.medscape.com/article/821863-overview#showall

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PLoS One • October 2014

Theobromine inhibits uric acid crystallization. A potential application in the treatment of uric acid nephrolithiasis

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Abstract

PURPOSE

To assess the capacity of methylxanthines (caffeine, theophylline, theobromine and paraxanthine) to inhibit uric acid crystallization, and to evaluate their potential application in the treatment of uric acid nephrolithiasis.

MATERIALS AND METHODS

The ability of methylxathines to inhibit uric acid nucleation was assayed turbidimetrically. Crystal morphology and its modification due to the effect of theobromine were evaluated by scanning electron microscopy (SEM). The ability of theobromine to inhibit uric acid crystal growth on calculi fragments resulting from extracorporeal shock wave lithotripsy (ESWL) was evaluated using a flow system.

RESULTS

The turbidimetric assay showed that among the studied methylxanthines, theobromine could markedly inhibit uric acid nucleation. SEM images showed that the presence of theobromine resulted in thinner uric acid crystals. Furthermore, in a flow system theobromine blocked the regrowth of post-ESWL uric acid calculi fragments.

CONCLUSIONS

Theobromine, a natural dimethylxanthine present in high amounts in cocoa, acts as an inhibitor of nucleation and crystal growth of uric acid. Therefore, theobromine may be clinically useful in the treatment of uric acid nephrolithiasis.

Full text, graphs, charts and 41 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4205022/

“This study represents the highest dose of theobromine studied in humans. We conclude that theobromine at normal intake ranges may contribute to the positive effects of chocolate, but at higher intakes, effects become negative.”

Psychopharmacology (Berlin) • July 2013

Psychopharmacology of theobromine in healthy volunteers

Author information

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Abstract

BACKGROUND

Theobromine, a methylxanthine related to caffeine and present in high levels in cocoa, may contribute to the appeal of chocolate. However, current evidence for this is limited.

OBJECTIVES

We conducted a within-subjects placebo-controlled study of a wide range of oral theobromine doses (250, 500, and 1,000 mg) using an active control dose of caffeine (200 mg) in 80 healthy participants.

RESULTS

Caffeine had the expected effects on mood including feelings of alertness and cardiovascular parameters. Theobromine responses differed according to dose; it showed limited subjective effects at 250 mg and negative mood effects at higher doses. It also dose-dependently increased heart rate. In secondary analyses, we also examined individual differences in the drug’s effects in relation to genes related to their target receptors, but few associations were detected.

CONCLUSIONS

This study represents the highest dose of theobromine studied in humans. We conclude that theobromine at normal intake ranges may contribute to the positive effects of chocolate, but at higher intakes, effects become negative.

Full text, graphs, charts and 51 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3672386/

Journal Of Clinical Psychopharmacology • August 2013

Effects of theobromine and caffeine on mood and vigilance

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Abstract

Like caffeine, theobromine crosses the blood-brain barrier and binds to adenosine receptors, suggesting it might share caffeine's beneficial effects on mood and vigilance. Therefore, the purpose of this study was to assess the effect of theobromine doses commonly found in foods on mood and vigilance parameters sensitive to caffeine. Caffeine was tested as a positive control. Twenty-four men (age, 23 [3] years) completed 6 double-blind trials during which they consumed experimental beverages, assessed their mood using standardized self-report questionnaires, and completed a 2-hour visual vigilance task. Three experimental doses (100, 200, and 400 mg theobromine) were delivered in a cocoa-based beverage; 3 matched control treatments (0 mg theobromine, 400 mg theobromine, and 100 mg caffeine) were delivered in a non-cocoa beverage. Mean salivary concentrations of theobromine exhibited significant dose-dependent differences (400 mg trials > 200 mg trial > 100 mg trial > 0 mg trials; $P < 0.005$). At every dose tested, theobromine failed to consistently affect mood state or vigilance ($P > 0.05$), but 100-mg caffeine significantly decreased lethargy/fatigue and increased vigor ($P = 0.006$ and 0.011, respectively). These findings indicate theobromine does not influence mood and vigilance when administered in nutritionally relevant doses, despite sharing many of caffeine's structural characteristics.

http://www.ncbi.nlm.nih.gov/pubmed/23764688

“Caffeine and theobromine are the most abundant methylxanthines in cacao and their physiological effects are notable. Their health-promoting benefits are so remarkable that chocolate is explored as a functional food.”

Nutrients • October 2013

Health benefits of methylxanthines in cacao and chocolate

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Abstract

One may wonder why methylxanthines are so abundant in beverages used by humans for centuries, or in cola-drinks that have been heavily consumed since their appearance. It is likely that humans have stuck to any brew containing compounds with psychoactive properties, resulting in a better daily life, i.e., more efficient thinking, exploring, hunting, etc., however, without the serious side effects of drugs of abuse. The physiological effects of methylxanthines have been known for a long time and they are mainly mediated by the so-called adenosine receptors. Caffeine and theobromine are the most abundant methylxanthines in cacao and their physiological effects are notable. Their health-promoting benefits are so remarkable that chocolate is explored as a functional food. The consequences of adenosine receptor blockade by natural compounds present in cacao/chocolate are here reviewed. Palatability and health benefits of methylxanthines, in general, and theobromine, in particular, have further contributed to sustain one of the most innocuous and pleasant habits: chocolate consumption.

Full text, 74 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3820066/

Handbook of Experimental Pharmacology • December 2011

Theobromine and the pharmacology of cocoa

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Abstract

The effects of theobromine in man are underresearched, possibly owing to the assumption that it is behaviourally inert. Toxicology research in animals may appear to provide alarming results, but these cannot be extrapolated to humans for a number of reasons. Domestic animals and animals used for racing competitions need to be guarded from chocolate and cocoa-containing foods, including foods containing cocoa husks. Research ought to include caffeine as a comparative agent, and underlying mechanisms need to be further explored. Of all constituents proposed to play a role in our liking for chocolate, caffeine is the most convincing, though a role for theobromine cannot be ruled out. Most other substances are unlikely to exude a psychopharmacological effect owing to extremely low concentrations or the inability to reach the blood-brain barrier, whilst chocolate craving and addiction need to be explained by means of a culturally determined ambivalence towards chocolate.

http://www.ncbi.nlm.nih.gov/pubmed/20859797

Food Chemical Toxicology • August 2009

Safety assessment of kola nut extract as a food ingredient

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Abstract

Kola nut extract is used in the food industry as a flavoring ingredient. Kola nut extract is derived from the seeds of primarily two tropical Cola species (Cola nitida (Vent.) Schott et Endl. or Cola acuminata (Beauv.) Schott et Endl.) of the Family, Sterculiaceae. Present day consumption of kola nut extract is 0.69 mg/kg/day. Caffeine and theobromine are two important constituents of kola nuts. Although limited biological data are available for kola nut extract specifically, the published data of the major constituents of kola nuts suggest the pharmacological/toxicological properties of kola nut extract, parallel to those of a roughly equivalent dose of caffeine. Frank developmental/reproductive effects have not been reported and changes in offspring cannot be extrapolated to humans. A NOEL/NOAEL cannot be defined for repeated oral exposure to kola nut extract from available data. Notwithstanding the foregoing, U.S. consumers have a history of safe consumption of cola-type beverages containing kola nut extract that dates at least to the late 19th Century, with a significant global history of exposure to the intact kola nuts that date centuries longer.

http://www.ncbi.nlm.nih.gov/pubmed/19394393

Journal Of Cerebral Blood Flow Metabolism • February 2008

Increases in cerebrospinal fluid caffeine concentration are associated with favorable outcome after severe traumatic brain injury in humans

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Abstract

Caffeine, the most widely consumed psychoactive drug and a weak adenosine receptor antagonist, can be neuroprotective or neurotoxic depending on the experimental model or neurologic disorder. However, its contribution to pathophysiology and outcome in traumatic brain injury (TBI) in humans is undefined. We assessed serial cerebrospinal fluid (CSF) concentrations of caffeine and its metabolites (theobromine, paraxanthine, and theophylline) by high-pressure liquid chromatography/ultraviolet in 97 ventricular CSF samples from an established bank, from 30 adults with severe TBI. We prospectively selected a threshold caffeine level of > or = 1 micromol/L (194 ng/mL) as clinically significant. Demographics, Glasgow Coma Scale (GCS) score, admission blood alcohol level, and 6-month dichotomized Glasgow Outcome Scale (GOS) score were assessed. Mean time from injury to initial CSF sampling was 10.77+/-3.13 h. On initial sampling, caffeine was detected in 24 of 30 patients, and the threshold was achieved in 9 patients. Favorable GOS was seen more often in patients with CSF caffeine concentration > or = versus < the threshold (55.6 versus 11.8%, P=0.028). Gender, age, admission CGS score, admission blood alcohol level, and admission systolic arterial blood pressure did not differ between patients with CSF caffeine concentration > or = versus < the threshold. Increases in CSF concentrations of the caffeine metabolites theobromine and paraxanthine were also associated with favorable outcome (P=0.018 and 0.056, respectively). Caffeine and its metabolites are commonly detected in CSF in patients with severe TBI and in an exploratory assessment are associated with favorable outcome. We speculate that caffeine may be neuroprotective by long-term upregulation of adenosine A1 receptors or acute inhibition of A2a receptors.

Full text, graphs, charts and 43 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714395/

“To our knowledge, this is the first report directly linking membrane potential changes to a single opening of an ion channel. Moreover, these events in cardiac cells suggest a possible additional mechanism by which caffeine and theophylline contribute to the generation of cardiac arrhythmias.”

American Journal Of Physiology And Heart Circulation Physiology • October 2007

Caffeine-activated large-conductance plasma membrane cation channels in cardiac myocytes: characteristics and significance

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Abstract

Caffeine-activated, large-conductance, nonselective cation channels (LCCs) have been found in the plasma membrane of isolated cardiac myocytes in several species. However, little is known about the effects of opening these channels. To examine such effects and to further understand the caffeine-activation mechanism, we carried out studies using whole-cell patch-clamp techniques with freshly isolated cardiac myocytes from rats and mice. Unlike previous studies, thapsigargin was used so that both the effect of opening LCCs and the action of caffeine were independent of Ca(2+) release from intracellular stores. These Ca(2+)-permeable LCCs were found in a majority of the cells from atria and ventricles, with a conductance of approximately 370 pS in rat atria. Caffeine and all its direct metabolic products (theophylline, theobromine, and paraxanthine) activated the channel, while isocaffeine did not. Although they share some similarities with ryanodine receptors (RyRs, the openings of which give rise to Ca(2+) sparks), LCCs also showed some different characteristics. With simultaneous Ca(2+) imaging and current recording, the localized fluorescence increase due to Ca(2+) entry through a single opening of an LCC (SCCaFT) was detected. When membrane potential, instead of current, was recorded, SCCaFT-like fluorescence transients (indicating single LCC openings) were found to accompany membrane depolarizations. To our knowledge, this is the first report directly linking membrane potential changes to a single opening of an ion channel. Moreover, these events in cardiac cells suggest a possible additional mechanism by which caffeine and theophylline contribute to the generation of cardiac arrhythmias.

Full text, graphs, charts and 57 references

http://ajpheart.physiology.org/content/ajpheart/293/4/H2448.full.pdf

Psychopharmacology (Berlin) • August 2005

Reinforcing effects of caffeine and theobromine as found in chocolate

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Abstract

RATIONALE

Although in a previous study we showed that caffeine and theobromine were the main psychopharmacologically active constituents in a 50-g bar of chocolate, mere activity does not guarantee a role in our liking for the food.

OBJECTIVES

Our aim was to see if liking for a drink repeatedly paired with these amounts of caffeine and theobromine would increase compared to a placebo-paired drink.

METHODS

Participants (n=64) consumed a 'novel' drink + treatment capsule on six non-consecutive mornings using a double-blind, placebo-controlled independent-sample design. Aspects of liking and intensity of various sensory descriptors for these drinks were measured at every drink collection. Treatment capsules contained either an ecologically relevant dose combination of 19-mg caffeine and 250-mg theobromine or a placebo.

RESULTS

Liking for the drink paired with the methylxanthine-containing capsules increased over time compared to the placebo-paired drink. This highly significant effect was confirmed by subjective, retrospective changes in liking for the drink.

CONCLUSIONS

Methylxanthines in amounts found in 50-g chocolate may well contribute to our liking for chocolate, especially to the more acquired taste for dark chocolate.

http://www.ncbi.nlm.nih.gov/pubmed/15772863

Psychopharmacology (Berlin) • November 2004

Methylxanthines are the psycho-pharmacologically active constituents of chocolate

Author information

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Abstract

RATIONALE

Liking, cravings and addiction for chocolate ("chocoholism") are often explained through the presence of pharmacologically active compounds. However, mere "presence" does not guarantee psycho-activity.

OBJECTIVES

Two double-blind, placebo-controlled studies measured the effects on cognitive performance and mood of the amounts of cocoa powder and methylxanthines found in a 50 g bar of dark chocolate.

METHODS

In study 1, participants (n=20) completed a test battery once before and twice after treatment administration. Treatments included 11.6 g cocoa powder and a caffeine and theobromine combination (19 and 250 mg, respectively). Study 2 (n=22) comprised three post-treatment test batteries and investigated the effects of "milk" and "dark" chocolate levels of these methylxanthines. The test battery consisted of a long duration simple reaction time task, a rapid visual information processing task, and a mood questionnaire.

RESULTS

Identical improvements on the mood construct "energetic arousal" and cognitive function were found for cocoa powder and the caffeine+theobromine combination versus placebo. In chocolate, both "milk chocolate" and "dark chocolate" methylxanthine doses improved cognitive function compared with "white chocolate". The effects of white chocolate did not differ significantly from those of water.

CONCLUSIONS

A normal portion of chocolate exhibits psychopharmacological activity. The identical profile of effects exerted by cocoa powder and its methylxanthine constituents shows this activity to be confined to the combination of caffeine and theobromine. Methylxanthines may contribute to the popularity of chocolate; however, other attributes are probably much more important in determining chocolate's special appeal and in explaining related self-reports of chocolate cravings and "chocoholism".

http://www.ncbi.nlm.nih.gov/pubmed/15549276

Journal Of Wildlife Discovery • April 2001

Theobromine intoxication in a red fox and a European badger in Sweden

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Abstract

A red fox (Vulpes vulpes) and a European badger (Meles meles) were found dead on a golf-course in October 1997 near Stockholm (Sweden). At necropsy, both animals were obese and the main finding was acute circulatory collapse. Theobromine intoxication was suspected as chocolate waste was available at a nearby farm and no other cause of death could be detected. Gastric contents and samples of liver from both animals were analyzed by reversed-phase high pressure liquid chromatography for the presence of methylxanthines. Theobromine and caffeine were detected in gastric contents and theobromine was identified in the liver samples from both animals. This appears to be the first report of theobromine intoxication in the red fox and the European badger.

http://www.ncbi.nlm.nih.gov/pubmed/11310889

Food Chemistry And Toxicology • June 1988

Methylxanthines: toxicity to humans - 1 - Theophylline

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Abstract

While there are several comprehensive reviews on the toxic effects of theophylline, caffeine and theobromine in animals, data on the toxicity of these methylxanthines in humans have not been extensively reviewed in one document. This question will be addressed in a series of three papers. This paper provides an overview of the human toxicity of theophylline. Only pertinent and recent information on theophylline toxicity is summarized. In addition, some information regarding the use and benefits of theophylline, the mechanism of its effects and factors that affect variability in its clearance and half-life is also provided. Some problems in the analytical methodology of theophylline, problems that may be responsible for the controversy in the reported dose-response effects, are critically reviewed.

http://www.ncbi.nlm.nih.gov/pubmed/3049277

Food Chemistry And Toxicology • July 1988

Methylxanthines: toxicity to humans - 2 - Caffeine

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Abstract

While there are several comprehensive reviews on the toxic effects of methylxanthines in animals, data on the toxicity of these chemicals in humans has not been extensively reviewed in one document. In a previous paper (Stavric, Fd Chem. Toxic. 1988, 26, 541), the toxicity of theophylline was reviewed. This paper, the second of three, is intended to provide an overview of the human toxicity of caffeine. Only pertinent and recent information on caffeine toxicity is summarized. In addition, some information regarding the benefits of caffeine and the mechanism of its effects is also provided. The use, effects and toxicity of caffeine intake are reviewed separately for different segments of the population. Controversy concerning the possible association of caffeine with fibrocystic disease of the breast and over the behavioural effects of the drug is presented briefly.

http://www.ncbi.nlm.nih.gov/pubmed/3053369

Food Chemistry And Toxicology • August 1988

Methylxanthines: toxicity to humans - 3 - chemicals Theobromine, paraxanthine and the combined effects of methylxanthines

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Abstract

This review provides a brief overview of known information on the human toxicity of theobromine and paraxanthine. Theobromine has some pharmacological effects, although these activities are considerably weaker than those of theophylline and/or caffeine, described in parts 1 and 2 of this series (Stavric, Fd Chem. Toxic. 1988, 26, 541 & 645). Paraxanthine, which is not found in plants or foods, is the major metabolite of caffeine in humans, in whom its toxicological potency appears to be very low. This paper gives a brief retrospective view of possible toxicological effects when methylxanthines are taken simultaneously or are present in combination as a result of metabolic transformation. Critical review of toxic manifestations due to exposure to relatively large doses of caffeine and theophylline indicates that such combined exposure may potentiate the toxic effects of either drug.

http://www.ncbi.nlm.nih.gov/pubmed/3058562

Food Chemistry And Toxicology • May 1986

Evaluation of the perinatal, postnatal and teratogenic effects of cocoa powder and theobromine in Sprague-Dawley/CD rats

Tarka SM Jr, Applebaum RS, Borzelleca JF.

Abstract

Studies were conducted to evaluate the effects of cocoa powder (CP) and theobromine (TBR) on perinatal and postnatal parameters and to assess their potential teratogenicity in the rat. In the peri/postnatal study, CP was given at 0, 2.5, 5.0 or 7.5% in the diet throughout gestation and lactation (postnatal day 21). In the teratology study, rats were given diets containing 0, 2.5 or 5.0% CP or 0.0675 or 0.135% TBR on days 6-19 of gestation. The CP-treated dams in the peri/postnatal study consumed significantly more food than did the controls during gestation. Weight gain was increased only in the 5.0 and 7.5% CP groups during lactation. Litter size was reduced slightly at 7.5% CP and pup survival was slightly decreased at 5.0 and 7.5% CP but none of these reductions was statistically significant. However, small but statistically significant decreases in pup body weights were noted in all treatment groups throughout lactation. In the teratology studies, rats given 2.5 or 5.0% CP or 0.0675 or 0.135% TBR consumed significantly more food than did the controls and the CP-treated dams gained significantly more weight. The percentage of pregnant dams and the mean number of corpora lutea were not affected by either CP or TBR. Foetuses exposed to 0.135 TBR had a significantly higher incidence of incompletely ossified or absent sternebrae and pubic bones, indicating a delay in osteogenesis. On the basis of the survival of treated offspring in the peri/postnatal study, these effects were not considered to be deleterious to either growth or survival. The effects are similar to those that have been reported elsewhere and been considered to indicate potential maternal or foetal toxicity that is unrelated to a specific compound/treatment. We conclude that any variations observed in these studies may be attributed to this non-specific maternal toxicity and are not related to the ingestion of either CP or TBR. The major methylxanthine found in the serum after CP or TBR ingestion was unchanged TBR and it did not bioaccumulate during gestation. The levels of CP and TBR used in these studies were more than 50 times greater than the maximum level of consumption by humans as reported in marketing surveys and were equivalent to a consumption of 10 lb of milk chocolate per day. The results indicate that neither CP nor TBR pose any health hazard to the developing foetus.

http://www.ncbi.nlm.nih.gov/pubmed/3744190

Food Chemistry & Toxicology • May 1986

Evaluation of the teratogenic potential of cocoa powder and theobromine in New Zealand White rabbits

Tarka SM Jr, Applebaum RS, Borzelleca JF.

Abstract

Studies were conducted to determine the teratogenic potential of theobromine (TBR) and cocoa powder (CP) in rabbits. TBR was given either by gavage at dose levels of 0, 25, 75, 125 or 200 mg/kg body weight/day or administered in the diet at 0, 0.0625, 0.125 or 0.1875% (approximately 0, 21, 41 or 63 mg/kg/day, respectively). CP was given at 2.5, 5.0 or 7.5% of the diet (approximately 25, 50 or 75 mg methylxanthines/kg body weight/day). The duration of exposure was from days 6 to 29 of gestation. Significant maternal mortality (40%) and reduced food consumption were observed at 200 mg TBR/kg/day. Mean foetal weights were similar to those of the control group at 25 or 75 mg TBR/kg/day, but decreases in foetal body weight and increases in various malformations and developmental variations were observed in groups given 125 or 200 mg/kg/day. Insufficient litters were available for examination in the 200-mg/kg/day dose group because of maternal toxicity/lethality (repetitive exposure by gavage to 200 mg TBR/kg approached the maternal LD50). In the dietary CP studies, three does died and three aborted, but these deaths and abortions were not treatment related. No maternal deaths occurred during dietary TBR exposure. Maternal weight gain and food consumption, and the mean number of corpora lutea were unaffected by either dietary CP or TBR. Neither foetotoxicity nor teratogenicity was associated with dietary ingestion of CP or TBR. The foetuses exposed to 0.125% or 0.1875% TBR had a significantly higher incidence of incompletely ossified or absent sternebrae, whereas exposure to 0.1875% or 7.5% CP resulted in corresponding effects on metacarpal bones, indicating a delay in osteogenesis. The predominant compound found in serum after TBR ingestion was unchanged TBR, and there was no evidence of bioaccumulation of TBR in serum during gestation. The highest levels of CP or TBR used in these studies was 38 times greater than the maximum consumption level reported for humans in marketing surveys, and corresponds to a consumption of greater than 7.5 lb milk chocolate/day.

http://www.ncbi.nlm.nih.gov/pubmed/25015017

“The theobromine-fed rats showed severe testicular atrophy with extensive spermatogenic cell degeneration and necrosis ...”

Food Chemistry And Toxicology • May 1984

Comparative toxicities of dietary caffeine and theobromine in the rat

By J. H. Gans

Abstract

Caffeine, incorporated into pulverized Purina Rat Chow at a concentration of 0.5%, was fed to male Sprague-Dawley rats for 7 or 8 wk and the effects were compared with those of 0.8% dietary theobromine, fed to male rats for 7 wk. Both dietary methylated xanthines produced significant decreases in food consumption and body-weight gain when compared to their respective control groups. Food consumption of caffeine-fed rats was 57.2% of controls and for theobromine-fed rats it was 77.9% of the respective controls. Theobromine produced significant decreases in thymus weights, with caffeine producing smaller decreases. The theobromine-fed rats showed severe testicular atrophy with extensive spermatogenic cell degeneration and necrosis, while the testes of rats fed caffeine for 7 or 8 wk showed only scattered vacuolar degeneration of spermatogenic cells. Caffeine appears to be more potent than theobromine as an anorexic agent in rats, but to be equivalent to theobromine in its potential for inducing thymic atrophy and spermatogenic cell destruction with testicular atrophy.

http://www.ncbi.nlm.nih.gov/pubmed/6539285

Progress In Clinical And Biological Research • July 1984

Methylxanthine composition and consumption patterns of cocoa and chocolate products

Shively CA, Tarka SM Jr.

Abstract

This chapter has compiled and evaluated the current information on the methylxanthine composition of cocoa and various chocolate foods and beverages, as well as the consumption pattern for these commodities. Although the earliest recorded reference to cacao was in 1502, it was not until 1876 that milk chocolate was invented, an event that formed the backbone of the chocolate industry today. The consumption of cocoa throughout the world has been influenced by a number of factors, and the period of peak consumption occurred during the early to mid-1960s when these factors were highly favorable. The greatest consumption of cocoa in metric tons over the past 10 yr has been in the United States, although the highest per capita consumer during this period was Switzerland. The African continent has been historically the primary producer of raw cocoa, with the Ivory Coast currently being the largest individual supplier. Limited marketing survey data is available for the consumption of methylxanthines in chocolate foods and beverages. In children and teenagers, the major dietary source of caffeine was found to be tea, followed by soft drinks and coffee, respectively. Although chocolate foods and beverages ranked the lowest of these dietary sources to provide caffeine, they do constitute the major source of dietary theobromine. Cacao is the major natural source of the xanthine base theobromine. Small amounts of caffeine are present in the bean along with trace amounts of theophylline. The methylxanthine content of beans varies with the varietal type, and is influenced by the fermentation process. Chocolate liquor is a semifinished product commonly called “baking” or “cooking” chocolate. The average theobromine and caffeine content of liquors has been reported at 1.2% and 0.21%, respectively. Cocoa powder, which is prepared after removal of the cocoa butter, contains about 1.9% theobromine and 0.21% caffeine. Chocolate beverages comprise the most widely studied category of chocolate products. Hot cocoa provides 62 mg/serving of theobromine and 4 mg/serving of caffeine when prepared from commercial instant mixes. Instant cold chocolate milk mixes supply an average of 58 mg/serving of theobromine and 5 mg/serving of caffeine. The methylxanthine content of chocolate foods has received only slight attention in the literature. The methylxanthine content of sweet chocolate ranges from 0.359 to 0.628% for theobromine and 0.017 to 0.125% for caffeine.

http://www.ncbi.nlm.nih.gov/pubmed/6396642

Critical Reviews In Toxicology • July 1982

The toxicology of cocoa and methylxanthines: a review of the literature

Author information

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Abstract

The critical review of the literature cited on pharmacology, toxicology, metabolism, and safety assessment clearly demonstrates that cocoa per se has not attracted a great deal of scientific interest because of its long-term usage with no reported adverse effects that would be injurious to man. On the other hand, a great deal of research has been directed towards understanding the pharmacological properties of the methylxanthines--caffeine, theobromine, and theophylline. Much of the emphasis on metabolism, toxicology, teratogenic potential, and safety assessment has been on the evaluation of caffeine. In light of the serious health concerns ascribed to the effects of caffeine and the lack of basic information on theobromine and theophylline, it is imperative that a major research program be undertaken to evaluate these methylxanthines and, of course, cocoa, coffee, and tea. It only will be through elucidating their mechanism of action that we will be in a position to assess their safety. Before committing research efforts to evaluating the long-term effects of these methylxanthines and their respective foodstuffs, which serve as our primary source of exposure, it is critical to initiate more basic research on the metabolism of caffeine, theophylline, and theobromine in several animal species and man. While published reports do appear in this area, it is essential to understand fully the similarities and differences between various animals and man. The influence of dietary factors and drug interactions must also be determined. Before establishing dosage levels for a chronic toxicity study, the pharmacokinetics of the dose must be determined in the species that will be used in long-term studies. This is necessary if there is a dose-dependency in the animal above which saturation may occur and the plasma half-life kinetics change, or shifts occur either in the metabolic pathways of degradation and/or in the route of excretion from the body. The area of teratology must also be thoroughly evaluated. Studies undertaken should include identification and quantitation of the metabolites of caffeine, theophylline, and theobromine in the pregnant animal, the respective pharmacokinetics of each compound, dose-dependency (if this is the case), and their potential teratogenicity. In addition, the influence of other drugs or dietary variables must be included. In addition to teratology, a great deal of research is needed to assess and quantitate fetal and neonatal metabolism of these compounds.

http://www.ncbi.nlm.nih.gov/pubmed/6765610

Journal Of Environmental Pathology And Toxicology • May 1978

Testicular atrophy and impaired spermatogenesis in rats fed high levels of the methylxanthines caffeine, theobromine, or theophylline

Weinberger MA, Friedman L, Farber TM,
Moreland FM, Peters EL, Gilmore CE, Khan MA.

Abstract

Experiments were designed to determine the effects of feeding the methylxanthines caffeine, theobromine, or theophylline to 4- to 6-week-old male rats at a dietary level of 0.5 percent for periods ranging from 14 to 75 weeks. In the first two experiments, Osborne-Mendel rats were fed the test substances alone or in combination with sodium nitrite to test the hypothesis that these amines might nitrosate in vivo to produce toxic nitrosamine compounds. The compounds failed to produce neoplastic or preneoplastic lesions, but a significant positive finding was the occurrence of severe bilateral testicular atrophy with aspermatogenesis or oligospermatogenesis in 85-100 percent of the rats fed caffeine or theobromine. In a third experiment the methylxanthines were fed to Holtzman rats for 19 weeks to determine whether testicular atrophy would be induced in a second strain of rat. The testicular effects were similar to those in Experiments I and II but were more pronounced. Caffeine and theobromine induced testicular injury in nearly all rats. Theophylline induced severe testicular atrophy in 14 percent of the rats, mild to moderate atrophy in 71 percent, and had no effect in 15 percent. The relative testicular toxicity of the methylxanthines was caffeine, most potent; theobromine, slightly less potent; and theophylline, considerably less potent. Somewhat variable atrophic changes of the accessory sexual organs (epididymis, prostate, and seminal vesicles) accompanied the testicular changes. Cytogenetic analysis of testes from caffeine- or theophylline-treated rats revealed a significantly reduced number of mitotic cells in the caffeine-treated group. Plasma testosterone concentrations were significantly elevated in the theobromine group and somewhat elevated in the caffeine-treated group; this correlated morphologically with an apparent hyperplasia of interstitial cells in severely atrophied testes in these groups. Plasma cholesterol concentrations were significantly increased in the caffeine and theobromine groups. Possible sites and mechanisms of actions of the methylxanthines in the induction of testicular atrophy and impaired spermatogenesis are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/722208

CHAPTER TWENTY

Diacetyl

The Peer Review

The current state of flavor is something of a paradox: On the one hand, Big Agriculture has drained "natural" foods of flavor in exchange for the convenience of cheap, year-round crops; on the other hand, "fake" foods are saturated (or "blasted," in the case of Goldfish) with laboratory developed super-perfect-flavors to make people crave them.

Synthetic flavors' earliest and biggest coup was turning vanilla from a coveted luxury good into a synonym for the bland and everyday. For two hundred years after its introduction to the West, vanilla was a precious commodity. Artificial pollination helped increase the global supply by allowing the plant to grow outside its native Mexico, but the real turning came in the 1870s, when scientists cracked the molecular structure of vanillin—and opened the floodgates for the manufacturing of synthetic vanilla flavor.

The turn of the 20th century then saw a massive boom in demand for vanilla bean, synthetic vanillin, and even plain sugar in the United States. This era is the beginning of a "mass consumer economy of sweetness," and mass anything in America means government regulation. Hence the Pure Food & Drug Act of 1906, which protected consumers from fraud—as well as health hazards—with measures like the country's first-ever statutory distinction between "genuine" and "imitation" foods. "Genuine" vanilla products, Congress reasoned, had to contain some derivative of vanilla bean; products with synthetic vanillin must be labeled "imitation," even though they might be more chemically pure than vanilla bean extracts diluted with other materials, as many were.

It took another two decades for chemists to invent what's arguably the world's most recognizable synthetic taste: butter. The neon stuff we pour over our popcorn to fuel a third viewing of Mad Max began as a simple solution to a complicated problem. As large-scale food manufacturing started gearing up in the 1920s, creameries realized that in order to sell a product on a national scale, it needed to taste both distinctive from other brands and the same as everything else marketed under the same name—not an easy feat when a single butter brand might use milk from dozens of different dairies.

Dutch chemists soon discovered that the compound diacetyl, produced either synthetically or by microorganisms, could add a "buttery" flavor to foods. Creameries then started adding a chemical that doesn't naturally occur in butter to actual butter in order to make it taste more like … butter. Our sense of what butter "tastes" like is in many ways shaped more by diacetyl, now found in everything from imitation butter, margarine, crackers and chips to movie theater popcorn, than the real deal.

In an odd turn of events, creameries began adding the compound diacetyl—which produces "buttery" flavor—to actual butter. The history of synthetic flavors is full of similar absurdities. Scientists only discovered that methyl anthranilate, the grape flavoring (and perfume ingredient) responsible for the deliciously fake taste of purple Jolly Ranchers, is actually in grapes until after it was widely used in products like NuGrape soda.

Native to American species like Concord grapes and responsible for the "foxiness"—wine experts' term of, say, Manischewitz—methyl anthranilate was initially used as grape flavoring for its wide availability. The chemical accuracy was purely coincidental.

Then there's peach flavor, which was only discovered thanks to an error in castor-oil production. Why was flavor synthesis, which is supposed to be, after all, a science, so haphazard? Partially because analysis is genuinely difficult; The compounds responsible for flavor are present in such small amounts that it takes nearly a ton of apples to yield just two grams of "apple flavor." Highly concentrated flavor molecules are also frequently volatile, poisonous, reactive, and simply difficult to work with.

Flavor production thus took a while to professionalize, but by the middle of the 20th century it had become a full-fledged field, complete with its own experts and full-time professionals. By then the consulting firm Arthur D. Little posited that "flavor leaders" like Coke and Heinz lacked aftertaste, encouraging consumers to eat more.

By the end of the '50s, the inevitable feeble backlash began. Congress passed the ineffective and outdated Food Additives Amendment, which imposed little more than stricter requirements for testing, in 1958. The following decade, the emerging counterculture affected food and other social mores and began the small minority of Americans with a long-standing phobia of artificial ingredients, and for good reason as pointed out in the following pages.

Toxicology And Applied Pharmacology • December 2015

Diacetyl and 2,3-pentanedione exposure of human cultured airway epithelial cells: Ion transport effects and metabolism of butter flavoring agents

Author information

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Abstract

Inhalation of butter flavoring by workers in the microwave popcorn industry may result in “popcorn workers’ lung.” In previous in vivo studies rats exposed for 6 h to vapor from the flavoring agents, diacetyl and 2,3-pentanedione, acquired flavoring concentration-dependent damage of the upper airway epithelium and airway hyporeactivity to inhaled methacholine. Because ion transport is essential for lung fluid balance,we hypothesized that alterations in ion transport may be an early manifestation of butter flavoring-induced toxicity. We developed a system to expose cultured human bronchial/tracheal epithelial cells (NHBEs) to flavoring vapors. NHBEs were exposed for 6 h to diacetyl or 2,3-pentanedione vapors (25 or ≥ 60 ppm) and the effects on short circuit current and transepithelial resistance (Rt) were measured. Immediately after exposure to 25 ppm both flavorings reduced Na+ transport,without affecting Cl- transport or Na+,K+-pump activity. Rt was unaffected. Na+ transport recovered 18 h after exposure. Concentrations (100-360 ppm) of diacetyl and 2,3-pentanedione reported earlier to give rise in vivo to epithelial damage, and 60 ppm, caused death of NHBEs 0 h post-exposure. Analysis of the basolateral medium indicated that NHBEs metabolize diacetyl and 2,3-pentanedione to acetoin and 2-hydroxy-3-pentanone, respectively. The results indicate that ion transport is inhibited transiently in airway epithelial cells by lower concentrations of the flavorings than those that result in morphological changes of the cells in vivo or in vitro.

Full text, graphs, charts and 38 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4739639/

“Diacetyl possesses a butter-like flavor and has been widely used as a flavoring agent. It forms from sugars and lipids via various bacteria and heat treatment in various foods and beverages, such as milk.”

Journal Of Agricultural Food Chemistry • May 2014

Mutagenicity of methylglyoxal in coffee

By T. Shibamoto

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Abstract

Diacetyl possesses a butter-like flavor and has been widely used as a flavoring agent. It forms from sugars and lipids via various bacteria and heat treatment in various foods and beverages, such as milk. The toxicity of diacetyl, especially when inhaled, has recently attracted the attention not only of consumers but also of regulatory agencies. Even though accurate quantitative analysis of diacetyl is extremely important in evaluating its possible adverse effects, precise quantitative analysis of diacetyl in foods and beverages, as well as in ambient air, is considerably difficult because it is highly reactive and soluble in water. Among the many analytical methods developed for measuring diacetyl, preparation of 2,3-dimethylquinoxaline followed by gas chromatography has been most commonly used in the analysis of various foods, beverages, and air samples. This mini-review summarizes the formation mechanisms, analytical methods, occurrence, and toxicity of diacetyl.

http://www.ncbi.nlm.nih.gov/pubmed/24738917

“... diacetyl inhalation increases Substance P levels in sensory nerves of airway epithelium. Because Substance P release in airways promotes inflammation and activation of sensory nerves mediates reflexes, neural changes may contribute to flavorings-related lung disease pathogenesis.”

Toxicology And Pathology • July 2014

Diacetyl increases sensory innervation and substance P production in rat trachea

Author information

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Mercer RR, Goldsmith WT, Jackson MC, Cumpston A, Frazer DG, Dey RD.
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Abstract

Inhalation of diacetyl, a butter flavoring, causes airway responses potentially mediated by sensory nerves. This study examines diacetyl-induced changes in sensory nerves of tracheal epithelium. Rats (n = 6/group) inhaled 0-, 25-, 249-, or 346-ppm diacetyl for 6 hr. Tracheas and vagal ganglia were removed 1-day postexposure and labeled for substance P (SP) or protein gene product 9.5 (PGP9.5). Vagal ganglia neurons projecting to airway epithelium were identified by axonal transport of fluorescent microspheres intratracheally instilled 14 days before diacetyl inhalation. End points were SP and PGP9.5 nerve fiber density (NFD) in tracheal epithelium and SP-positive neurons projecting to the trachea. PGP9.5-immunoreactive NFD decreased in foci with denuded epithelium, suggesting loss of airway sensory innervation. However, in the intact epithelium adjacent to denuded foci, SP-immunoreactive NFD increased from 0.01 ± 0.002 in controls to 0.05 ± 0.01 after exposure to 346-ppm diacetyl. In vagal ganglia, SP-positive airway neurons increased from 3.3 ± 3.0% in controls to 25.5 ± 6.6% after inhaling 346-ppm diacetyl. Thus, diacetyl inhalation increases SP levels in sensory nerves of airway epithelium. Because SP release in airways promotes inflammation and activation of sensory nerves mediates reflexes, neural changes may contribute to flavorings-related lung disease pathogenesis.

Full Text, graphs, charts and 55 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4637165/

“Diacetyl (DA), a component of artificial butter flavoring, has been linked to the development of bronchiolitis obliterans (BO), a disease of airway epithelial injury and airway fibrosis.”

American Journal Of Respiratory, Cellular And Molecular Biology • October 2014

Diacetyl induces amphiregulin shedding in pulmonary epithelial cells and in experimental bronchiolitis obliterans

Author information

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Kummarapurugu AB, Zhang HL, Nugent JL, Beasley RF,
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Abstract

Diacetyl (DA), a component of artificial butter flavoring, has been linked to the development of bronchiolitis obliterans (BO), a disease of airway epithelial injury and airway fibrosis. The epidermal growth factor receptor ligand, amphiregulin (AREG), has been implicated in other types of epithelial injury and lung fibrosis. We investigated the effects of DA directly on the pulmonary epithelium, and we hypothesized that DA exposure would result in epithelial cell shedding of AREG. Consistent with this hypothesis, we demonstrate that DA increases AREG by the pulmonary epithelial cell line NCI-H292 and by multiple independent primary human airway epithelial donors grown under physiologically relevant conditions at the air-liquid interface. Furthermore, we demonstrate that AREG shedding occurs through a TNF-ß-converting enzyme (TACE)-dependent mechanism via inhibition of TACE activity in epithelial cells using the small molecule inhibitor, TNF-ß protease inhibitor-1, as well as TACE-specific small inhibitor RNA. Finally, we demonstrate supportive in vivo results showing increased AREG transcript and protein levels in the lungs of rodents with DA-induced BO. In summary, our novel in vitro and in vivo observations suggest that further study of AREG is warranted in the pathogenesis of DA-induced BO.

Full text, graphs, charts and 23 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4189481/

“... the upper and lower extrapulmonary airways are of similar sensitivity to inhaled electrophilic vapors. Dosimetrically based extrapolation of nasal responses in nose-breathing rodents may provide an approach to predict risk to the lower airways of humans during mouth-breathing.”

Toxicology Science • November 2014

Tissue sensitivity of the rat upper and lower extrapulmonary airways to the inhaled electrophilic air pollutants diacetyl and acrolein

Author information
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Abstract

The target site for inhaled vapor-induced injury often differs in mouth-breathing humans compared with nose-breathing rats, thus complicating the use of rat inhalation toxicity data for assessment of human risk. We sought to examine sensitivity of respiratory/transitional nasal (RTM) and tracheobronchial (TBM) mucosa to two electrophilic irritant vapors: diacetyl and acrolein. Computational fluid dynamic physiologically based pharmacokinetic modeling was coupled with biomarker assessment to establish delivered dose-response relationships in RTM and TBM in male F344 rats following 6 h exposure to diacetyl or acrolein. Biomarkers included glutathione status, proinflammatory and antioxidant gene mRNA levels, and nuclear translocation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Modeling revealed that 0.0094-0.1653 µg acrolein/min-cm(2) and 3.9-21.6 µg diacetyl/min-cm(2) were deposited into RTM/TBM. Results indicate RTM and TBM were generally of similar sensitivity to diacetyl and acrolein. For instance, both tissues displayed induction of antioxidant and proinflammatory genes, and nuclear accumulation of Nrf2 after electrophile exposure. Hierarchical cellular response patterns were similar in RTM and TBM but differed between vapors. Specifically, diacetyl exposure induced proinflammatory and antioxidant genes concomitantly at low exposure levels, whereas acrolein induced antioxidant genes at much lower exposure levels than that required to induce proinflammatory genes. Generally, diacetyl was less potent than acrolein, as measured by maximal induction of transcripts. In conclusion, the upper and lower extrapulmonary airways are of similar sensitivity to inhaled electrophilic vapors. Dosimetrically based extrapolation of nasal responses in nose-breathing rodents may provide an approach to predict risk to the lower airways of humans during mouth-breathing.

Full text, graphs, charts and 44 references

http://toxsci.oxfordjournals.org/content/142/1/126.long

“when manufactured for use as a synthetic flavouring/additive in processed foods (e.g. microwave popcorn), it [Diacetyl] poses a human health threat ...”

Review • December 2014

Diacetyl Exposure As A Pneumotoxic Factor

Beata Starek-Swiechowicz, Andrzej Starek*

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Abstract

Diacetyl (2,3-butanedione) is a natural ingredient in foodstuffs which is not generally regarded health risk to consumers. Nevertheless, when manufactured for use as a synthetic flavouring/additive in processed foods (e.g. microwave popcorn), it poses a human health threat at the workplace. Its pneumotoxic action consists of inflammation, obstruction and restriction in the distal respiratory tract. One of the factors causing bronchiolitis obliterans is also recognised to be diacetyl. The scientific literature mostly describes human exposure to diacetyl in factory settings where functional disorders and structural changes of the respiratory system have been recorded, particularly bronchiolitis obliterans. Moreover, differential diagnosis shows pathological changes in the distal respiratory tract and in the pneumotoxic actions of diacetyl.

PDF at this link, top right corner of page

Graphs, charts and 41 references

http://www.ncbi.nlm.nih.gov/pubmed/25272573

“The butter flavorant, diacetyl, forms a covalent adduct with 2-deoxyguanosine, uncoils DNA, and leads to cell death.”

Journal Of Agricultural And Food Chemistry • March 2012

The butter flavorant, diacetyl, forms a covalent adduct with 2-deoxyguanosine, uncoils DNA, and leads to cell death

Author information

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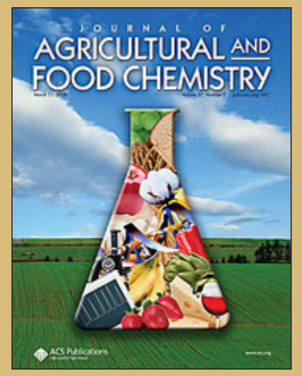
Abstract

Diacetyl (DA), a natural butter flavorant, is a causative agent for the lung disease obliterative bronchiolitis. Mutagenic properties of 1,2-dicarbonyls have previously been empirically linked to their possible interaction with DNA nucleobases. This study for the first time identifies chemically the adduct of DA with 2-deoxyguanosine. Selective reactivity of DA with 5’-TTTGTTTTT-3’ over 5’-TTTTTTTTT-3’ indicated its propensity to modify specifically the guanosine residue. Treatment of plasmid DNA, pBR322, with DA induced changes in electrophoretic mobility that are typical of ternary structure disruption. Such DNA nucleobase interaction of DA translated into increased apoptosis in DA-treated SH-SY5Y cells in a dose-dependent manner (IC(50) = 0.114 ± 0.0421 mM). The traditional carbonyl scavengers metformin, 2-thiobarbituric acid, and d-penicillamine protected cells from DA toxicity in proportion to their rates of reaction with DA, with d-penicillamine causing a maximal increase in the IC(50) to 5.23 ± 0.0992 mM when co-incubated with DA.



http://www.ncbi.nlm.nih.gov/pubmed/22385266

“In light of the chronic exposure of industry workers to Diacetyl, this study raises the troubling possibility of long-term neurological toxicity mediated by Diacetyl.”

Chemical Research In Toxicology • October 2012

The butter flavorant, diacetyl, exacerbates ß-amyloid cytotoxicity

Author information

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Abstract

Diacetyl (DA), an ubiquitous butter-flavoring agent, was found to influence several aspects of amyloid-ß (Aß) aggregation--one of the two primary pathologies associated with Alzheimer’s disease. Thioflavin T fluorescence and circular dichroism spectroscopic measurements revealed that DA accelerates $A\beta_{1-42}$ aggregation into soluble and ultimately insoluble ß-pleated sheet structures. DA was found to covalently bind to Arg^5 of $A\beta_{1-42}$ through proteolytic digestion-mass spectrometric experiments. These biophysical and chemical effects translated into the potentiation of $A\beta_{1-42}$ cytotoxicity by DA toward SH-SY5Y cells in culture. DA easily traversed through a MDR1-MDCK cell monolayer, an in vitro model of the blood-brain barrier. Additionally, DA was found not only to be resistant to but also inhibitory toward glyoxalase I, the primary initiator of detoxification of amyloid-promoting reactive dicarbonyl species that are generated naturally in large amounts by neuronal tissue. In light of the chronic exposure of industry workers to DA, this study raises the troubling possibility of long-term neurological toxicity mediated by DA.

http://www.ncbi.nlm.nih.gov/pubmed/22731744

DIACETYL

Diacetyl and related compounds produce the buttery odor and flavor of many foods. It occurs as a natural byproduct of fermentation and is found in several dairy products like butter, cheese and milk as well as in bread, coffee, brandy, and rum.

Diacetyl is an organic substance that imparts a rich, buttery flavor. Although it occurs naturally in some foods, most of the diacetyl in the human diet is artificially manufactured and used to flavor processed food products.

Major Sources

Diacetyl is the main flavoring agent in margarine, shortening, oil sprays and most other artificially flavored butter substitutes. It’s widely used in microwave popcorn, potato chips, corn chips and crackers, but it’s also frequently found in cookies, chocolate, cocoa-flavored products, candy, gelatin desserts, flour mixes, flavored syrups and prepackaged frosting. Sauces, soft drinks, chewing gum and ice cream are other common sources.

Other Sources

Diacetyl is found in real butter, too. It’s the main flavor agent in the starter cultures used to make butter, according to a report by the National Toxicology Program. Minute amounts of the compound are also naturally present in milk, yogurt, cheese, coffee, honey and most fruits. Because diacetyl is a natural product of alcohol fermentation, it is often found in beer and wine.

On food labels, when Diacetyl is used or present it is typically listed under the blanket term “artificial flavors.”

Clinical Chest Medicine • December 2012

Newly recognized occupational and environmental causes of chronic terminal airways and parenchymal lung disease

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Abstract

“With the introduction of new materials and changes in manufacturing practices, occupational health investigators continue to uncover associations between novel exposures and chronic forms of diffuse parenchymal lung disease and terminal airways disease. To discern exposure-disease relationships, clinicians must maintain a high index of suspicion for the potential toxicity of occupational and environmental exposures. This article details several newly recognized chronic parenchymal and terminal airways. Diseases related to exposure to indium, nylon flock, diacetyl used in the flavorings industry, nanoparticles, and the World Trade Center disaster are reviewed. Also reviewed are methods in worker surveillance and the potential use of biomarkers in the evaluation of exposure-disease relationships.”

Full text, photos and 69 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3515663/

“Like diacetyl, 2,3-pentanedione caused fibrosis of the small airways.”

Environmental Health Perspectives • December 2012

Still Searching for Better Butter Flavoring

By Carol Potera

After diacetyl (2,3-butanedione) was shown to cause bronchiolitis obliterans in workers who inhaled high levels of this volatile butter flavoring at microwave popcorn processing plants,1,2,3 some manufacturers switched to a substitute assumed to be safer. Recent rodent studies, however, suggest that the substitute, 2,3-pentanedione, may be as damaging to the respiratory tract as the diacetyl it replaced.4,5

Bronchiolitis obliterans, or “popcorn lung,” is a rare, irreversible, debilitating lung disease in which inflammation and scarring obstruct the smallest airways, the bronchioles. There is no good treatment for the disease short of a lung transplant.6 Ironically, lung transplant itself can trigger bronchiolitis obliterans through organ rejection mechanisms, limiting the survival of many transplant patients.7

After the disease was identified in popcorn workers, researchers at the National Institute for Occupational Safety and Health (NIOSH) reported bronchial epithelial damage in rats inhaling vapors of butter flavoring.8 This type of injury causes fibrosis (thickening and scarring) of the bronchioles, which is the underlying cause of bronchiolitis obliterans. In 2008 some of the same NIOSH researchers narrowed their studies to diacetyl, a major component of butter flavoring vapors, and reported similar acute damage in rats.9 The same year, Daniel Morgan, head of the Respiratory Toxicology Group at the National Institute of Environmental Health Sciences, and colleagues reported that mice develop bronchial epithelial damage after inhaling diacetyl vapors at concentrations equivalent to worker exposures.6 Rats proved even more susceptible than mice and developed full-blown bronchiolitis obliterans after repeated exposure to diacetyl.4,10

Because diacetyl and 2,3-pentanedione, both diketones, are chemically very similar, Morgan suspected that inhaled 2,3-pentanedione may be toxic to the respiratory tract as well. He exposed rats to up to 200 ppm of 2,3-pentanedione for either 10 or 12 days, using the same doses and exposure times as the earlier diacetyl rat experiments. Like diacetyl, 2,3-pentanedione caused fibrosis of the small airways.

Full text, graphs, charts and 12 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3548289/

Journal Of Occupational And Environmental Hygiene • February 2011

Identification and measurement of diacetyl substitutes in dry bakery mix production

Author information

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Abstract

In 2008, a company using multiple buttermilk flavorings in the production of dry bakery mixes replaced one liquid flavoring containing 15-20% diacetyl with a proprietary substitute meant to lower occupational risk for diacetyl-related bronchiolitis obliterans. Subsequently, the National Institute for Occupational Safety and Health (NIOSH) evaluated buttermilk flavoring-related exposures at this company's facility, with a focus on measuring ketones by several methods. Volatile organic compounds (VOCs) were evaluated in the headspaces of six bulk flavorings samples, including the substitute buttermilk flavoring. Ketones were evaluated in workplace air via area and personal samples collected during batch preparation of the substitute buttermilk flavoring and production of a bakery mix containing the same flavoring. Air samples were evaluated using five different methods: NIOSH 2549, Modified OSHA PV2118, OSHA 1013, NIOSH Draft Procedure SMP2, and evacuated canisters. Of five buttermilk flavorings from five different flavorings manufacturers, diacetyl was present in four, including the substitute flavoring; acetoin in two; 2,3-pentanedione in four; 2,3-hexanedione in one; and 2,3-heptanedione in three. Among material safety data sheets (MSDS) for four flavorings, only one listed a hazardous ingredient, which was acetoin. The predominant flavoring ingredient identified in the headspace of the substitute flavoring was 2,3-pentanedione; all other chemicals noted above were also present. Diacetyl and 2,3-pentanedione were measured in workplace air via evacuated canisters. In one area and one personal air sample, 2,3-pentanedione was measured by OSHA Method 1013 at concentrations of 78 and 91 ppb, respectively. Without their or the employer's knowledge, workers who used buttermilk flavorings were exposed to substitute ketones from many flavorings manufacturers. Because 2,3-pentanedione, 2,3-hexanedione, and 2,3-heptanedione all share the same functional ß-diketone group as diacetyl, these compounds also may share diacetyl's mechanism of toxicity. Until more is known about 2,3-pentanedione and other ß-diketone compounds, they should not be assumed to be safe. Companies using artificial buttermilk flavorings should use a precautionary approach that assumes these flavorings pose a health risk and limit exposures through engineering and administrative controls and use of personal protective equipment.

http://www.ncbi.nlm.nih.gov/pubmed/21253982

International Journal Of Occupational Environmental Health • April 2011

A proposal for a safe exposure level for diacetyl

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Abstract

“Diacetyl is a naturally occurring compound that has been used in concentrated form as a food additive, particularly in butter flavorings. Inhalation of diacetyl and butter flavoring fumes has caused a variety of respiratory diseases in workers and consumers including bronchiolitis obliterans (BO), a relatively rare, severe, and irreversible lung disease. A safe level of exposure to diacetyl has not been established. We review the literature on diacetyl and flavoring toxicity and critique a recent proposal for an occupational exposure limit (OEL) of 0.2 ppm for diacetyl. We present unpublished data and novel analyses in support of our proposal for a safe level of exposure. Our findings indicate that a safe level of exposure exists around or below a time-weighted average of 1 ppb for an eight-hour workday. **The levels of exposure we found to be unsafe include ranges that popcorn consumers may potentially be exposed to, indicating a risk of severe lung disease (including BO) [bronchiolitis obliterans] for some consumers.**”

http://www.ncbi.nlm.nih.gov/pubmed/21618944

“Extrapolation to the human via the model suggested that inspired diacetyl may penetrate to the intrapulmonary airways to a greater degree in the human than in the rat. Thus, based on dosimetric relationships, extrapulmonary airway injury in the rat may be predictive of intrapulmonary airway injury in humans.”

Toxicology Science • March 2009

Inhalation dosimetry of diacetyl and butyric acid, two components of butter flavoring vapors

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Abstract

Occupational exposure to butter flavoring vapors (BFV) is associated with significant pulmonary injury. The goal of the current study was to characterize inhalation dosimetric patterns of diacetyl and butyric acid, two components of BFV, and to develop a hybrid computational fluid dynamic-physiologically based pharmacokinetic model (CFD-PBPK) to describe these patterns. Uptake of diacetyl and butyric acid vapors, alone and in combination, was measured in the upper respiratory tract of anesthetized male Sprague-Dawley rats under constant velocity flow conditions and the uptake data were used to validate the CFD-PBPK model. Diacetyl vapor (100 or 300 ppm) was scrubbed from the airstream with 76-36% efficiency at flows of 100-400 ml/min. Butryic acid (30 ppm) was scrubbed with >90% efficiency. Concurrent exposure to butyric acid resulted in a small but significant reduction of diacetyl uptake (36 vs. 31%, $p < 0.05$). Diacetyl was metabolized in nasal tissues in vitro, likely by diacetyl reductase, an enzyme known to be inhibited by butyric acid. The CFD-PBPK model closely described diacetyl uptake; the reduction in diacetyl uptake by butyric acid could be explained by inhibition of diacetyl reductase. Extrapolation to the human via the model suggested that inspired diacetyl may penetrate to the intrapulmonary airways to a greater degree in the human than in the rat. Thus, based on dosimetric relationships, extrapulmonary airway injury in the rat may be predictive of intrapulmonary airway injury in humans. Butyric acid may modulate diacetyl toxicity by inhibiting its metabolism and/or altering its inhalation dosimetric patterns.

Full text, graphs, charts and 49 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2644402/

“The no-observed-effect levels for each effect in the mice were above 100 ppm and initiation of sensory irritation in humans was estimated to occur above 20 ppm. No acute warning signal from the airways is expected at diacetyl levels that have caused bronchiolitis obliterans and other toxic effects. The sensory irritation effect, which occurred rapidly upon initiation of exposure, faded rapidly. Furthermore, high-level diacetyl exposures decreased the sensory irritation warning signal in mice upon repeated exposure, which suggests that the compound is especially insidious.”

Inhalation Toxicology • November 2009

Acute airway effects of diacetyl in mice

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Abstract

Occupational exposures to the butter flavouring agent diacetyl (2,3-butanedione) have caused lung inflammation and severe airflow limitation due to bronchiolitis obliterans. Diacetyl is naturally present in butter, beer, white wine, etc., and its pleasant odour is easily recognized by consumers. However, this pleasant odour may induce a false sense of safety when higher airborne concentrations are encountered in industrial use. In this study, the acute warning properties, in terms of sensory irritation, that could be useful to prevent workers from exposures to a high concentration were first investigated in a mouse bioassay. Then at higher exposure concentrations, the possibility of airflow limitation and pulmonary irritation were studied with the same mouse bioassay. Diacetyl induces concentration-dependent irritation in all parts of the respiratory tract during a 2-h exposure period. The no-observed-effect levels for each effect in the mice were above 100 ppm and initiation of sensory irritation in humans was estimated to occur above 20 ppm. No acute warning signal from the airways is expected at diacetyl levels that have caused bronchiolitis obliterans and other toxic effects. The sensory irritation effect, which occurred rapidly upon initiation of exposure, faded rapidly. Furthermore, high-level diacetyl exposures decreased the sensory irritation warning signal in mice upon repeated exposure, which suggests that the compound is especially insidious.

http://www.ncbi.nlm.nih.gov/pubmed/19852554

“These findings are consistent with the conclusion that inhaled diacetyl is a respiratory hazard.”

Toxicology And Pathology • February 2008

Respiratory toxicologic pathology of inhaled diacetyl in sprague-dawley rats

Author information

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Abstract

Inhalation of butter flavoring vapors by food manufacturing workers causes an emerging lung disease clinically resembling bronchiolitis obliterans. Diacetyl, an alpha-diketone, is a major component of these vapors. In rats, we investigated the toxicity of inhaled diacetyl at concentrations of up to 365 ppm (time weighted average), either as six-hour continuous exposures or as four brief, intense exposures over six hours. A separate group inhaled a single pulse of ~1800 ppm diacetyl (92.9 ppm six-hour average). Rats were necropsied 18 to 20 hours after exposure. Diacetyl inhalation caused epithelial necrosis and suppurative to fibrinosuppurative inflammation in the nose, larynx, trachea, and bronchi. Bronchi were affected at diacetyl concentrations of 294.6 ppm or greater; the trachea and larynx were affected at diacetyl concentrations of 224 ppm or greater. Both pulsed and continuous exposure patterns caused epithelial injury. The nose had the greatest sensitivity to diacetyl. Ultrastructural changes in the tracheal epithelium included whorling and dilation of the rough endoplasmic reticulum, chromatin clumping beneath the nuclear membrane, vacuolation, increased inter-cellular space and foci of denuded basement membrane. Edema and hemorrhage extended into the lamina propria. These findings are consistent with the conclusion that inhaled diacetyl is a respiratory hazard.

http://www.ncbi.nlm.nih.gov/pubmed/18474946

“These results suggest that Diacetyl and Glyoxal have potential tumor-promoting activities and may also have initiating activities in carcinogenesis in the glandular stomach.”

Japanese Journal of Cancer Research GANN • March 2008

Potential Initiating And Promoting Activities Of Diacetyl And Glyoxal In Rat Stomach Mucosa

By Chie Furihata, Sayuri Yoshida and Taijiro Matsushima
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Abstract

The potential initiating and promoting activities in the rat glandular stomach of the dicarbonyl compounds diacetyl (DA) and glyoxal (G), which are found in various heated foods, were studied. Administration of DA at doses of 300 to 1500mg/kg body weight and of G at doses of 150 to 400mg/kg body weight by gastric intubation to male F344 rats induced up to 100-fold increase in ornithine decarboxylase activity (formation of 195 pmol CO2/30min/mg protein by DA and 302 pmol CO2/30min/mg protein by G) with maxima after 16hr. These treatments also induced a more than 10-fold increase in DNA synthesis (incorporation of 11, 400 dpm of [3H]dThd/μ g DNA by DA and 15, 100dpm of [3H]dThd/μ g DNA by G) with maxima after 16hr, and induced apparent unscheduled DNA synthesis in the pyloric mucosa of the stomach within 3hr after administration. These results suggest that DA and G have potential tumor-promoting activities and may also have initiating activities in carcinogenesis in the glandular stomach.

Full text, PDF with references

https://www.jstage.jst.go.jp/article/cancersci1985/76/9/76_9_809/_pdf

“Depending on the route and duration of exposure, diacetyl causes significant epithelial injury, peribronchial lymphocytic inflammation, or fibrohistiocytic lesions in the terminal bronchioles. Collectively these results indicate that clinically relevant diacetyl exposures result in a pattern of injury that replicates features of human obliterative bronchiolitis.”

Toxicology Science • May 2008

Respiratory toxicity of diacetyl in C57BL/6 mice

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Abstract

Diacetyl, a component of artificial butter flavoring, is a potential etiological agent of obliterative bronchiolitis (OB); however, the toxic dose and mechanisms of toxicity remain controversial. We evaluated the respiratory toxicity of diacetyl in a murine model using several exposure profiles relevant to workplace conditions at microwave popcorn packaging plants. Male C57Bl/6 mice were exposed to inhaled diacetyl across several concentrations and duration profiles, or by direct oropharyngeal aspiration. Effects of diacetyl on the respiratory tract were evaluated by histopathology and BALF analyses. Subacute exposure to 200 or 400 ppm diacetyl for 5 days caused deaths, necrotizing rhinitis, necrotizing laryngitis and bronchitis. Reducing the exposure to 1 h/day (100, 200, 400 ppm) for 4 weeks resulted in less nasal and laryngeal toxicity, but led to peribronchial and peribronchiolar lymphocytic inflammation. A similar pattern was observed with intermittent high-dose exposures at 1200 ppm (15 min, twice a day, 4 weeks). Subchronic exposures to 100 ppm (6 h/day, 12 weeks) caused moderate nasal injury, and peribronchial lymphocytic inflammation accompanied by epithelial atrophy, denudation, and regeneration. Treatment with 400 mg/kg by oropharyngeal aspiration to bypass the nose caused foci of fibrohistiocytic proliferation with little or no inflammation at the junction of the terminal bronchiole and alveolar duct. Depending on the route and duration of exposure, diacetyl causes significant epithelial injury, peribronchial lymphocytic inflammation, or fibrohistiocytic lesions in the terminal bronchioles. Collectively these results indicate that clinically relevant diacetyl exposures result in a pattern of injury that replicates features of human OB.

Full text, photos, graphs, charts and 28 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2669658/

“The increase in the frequency of small colonies in the assay with diacetyl indicates that diacetyl causes damage to multiple loci on chromosome 11 in addition to functional loss of the thymidine kinase locus.”

Food And Chemical Toxicology • August 2008

Evaluation of the butter flavoring chemical diacetyl and a fluorochemical paper additive for mutagenicity and toxicity using the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells

Author information

Whittaker P1, Clarke JJ, San RH, Begley TH, Dunkel VC.

Abstract

Diacetyl (2,3-butanedione) is a yellowish liquid that is usually mixed with other ingredients to produce butter flavor or other flavors in a variety of food products. Inhalation of butter flavoring vapors was first associated with clinical bronchiolitis obliterans among workers in microwave popcorn production. Recent findings have shown irreversible obstructive lung disease among workers not only in the microwave popcorn industry, but also in flavoring manufacture, and in chemical synthesis of diacetyl, a predominant chemical for butter flavoring. It has been reported that perfluorochemicals utilized in food packaging are migrating into foods and may be sources of oral exposure. Relatively small quantities of perfluorochemicals are used in the manufacturing of paper or paperboard that is in direct contact with food to repel oil or grease and water. Because of recent concerns about perfluorochemicals such as those found on microwave popcorn bags (e.g. Lodyne P208E) and diacetyl in foods, we evaluated both compounds for mutagenicity using the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells. Lodyne P208E was less toxic than diacetyl and did not induce a mutagenic response. Diacetyl induced a highly mutagenic response in the L5178Y mouse lymphoma mutation assay in the presence of human liver S9 for activation. The increase in the frequency of small colonies in the assay with diacetyl indicates that diacetyl causes damage to multiple loci on chromosome 11 in addition to functional loss of the thymidine kinase locus.

http://www.ncbi.nlm.nih.gov/pubmed/18585428

International Journal Of Occupational And Environmental Health • January 2007

Popcorn-worker lung caused by corporate and regulatory negligence — an avoidable tragedy

Author information

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Abstract

“Diacetyl-containing butter flavor was identified as the cause of an outbreak of bronchiolitis obliterans (BO) and other lung diseases in popcorn-plant workers. Litigation documents show that the outbreak was both predictable and preventable. The industry trade organization was aware of BO cases in workers at butter-flavoring and popcorn-manufacturing plants but often failed to implement industrial hygiene improvements and actively hid pertinent warning information. Due to weaknesses in the organization and mandates of regulatory bodies, organizations such as NIOSH, OSHA, the FDA, particularly the “generally recognized as safe” (GRAS) system, and the EPA failed to detect and prevent the outbreak, which highlights the need for systemic changes in food-product regulation, including the need for corporations to act responsibly, for stronger regulations with active enforcement, for a restructuring of the GRAS system, and for criminal penalties against corporations and professionals who knowingly hide information relevant to worker protection.”

http://www.ncbi.nlm.nih.gov/pubmed/17427353

Current Opinion In Allergy And Clinical Immunology • April 2007

Flavoring-related bronchiolitis obliterans

By K. Kreiss

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Abstract

PURPOSE OF REVIEW

In 2000, inhalation of butter flavoring vapors was first associated with clinical bronchiolitis obliterans among workers in microwave popcorn production. Toxicologic and epidemiologic studies in the succeeding 5 years have intervention and research implications.

RECENT FINDINGS

Irreversible obstructive disease exists in workers throughout the microwave popcorn industry, in flavoring manufacture, and in the chemical synthesis of diacetyl, a predominant chemical in butter flavoring. Biologic plausibility of the role of diacetyl and other components of butter flavoring in causing bronchiolitis obliterans exists in rodent experiments which demonstrate respiratory epithelial necrosis. Some risky jobs were associated with short-term peak flavoring exposures, and average 8-h diacetyl exposures as low as 0.02 parts per million were measured in a work area where disease occurred in workers mixing butter flavorings with heated oil.

SUMMARY

Until safe levels of flavoring chemicals are determined, prevention requires substitution, engineering controls, improved work practices, and personal protective equipment to lower exposure, in conjunction with medical surveillance for accelerated declines in pulmonary function. An epidemiologic approach to longitudinal medical surveillance and flavoring chemical exposures, paired with inhalation toxicology studies of flavoring components, will lay the basis for determining health-protective exposure limits for various flavoring chemicals.

http://www.ncbi.nlm.nih.gov/pubmed/17351470

Archives In Toxicology • March 2005

Role of diacetyl metabolite in alcohol toxicity and addiction via electron transfer and oxidative stress

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Abstract

“There are many gaps in our knowledge of the molecular basis of alcohol toxicity and addiction. Metabolism affords mainly acetic acid via acetaldehyde. A minor metabolite, diacetyl (an alpha-dicarbonyl), arises from the aldehyde. We propose that this C(4) entity and/or its iminium derivatives from condensation with protein amino groups plays important roles in bioresponses. A review of the literature reveals substantial support for this premise. Reduction potentials for diacetyl and its iminium derivatives fall in the range favorable for catalytic electron transfer in vivo, which can generate oxidative stress via reactive oxygen species due to redox cycling. Oxidative stress and reactive oxygen species are linked to toxicity associated with major organs by alcohol. The alpha-dicarbonyl moiety in related substances is believed to induce various toxic responses, such as Alzheimer’s disease, mutagenesis, and carcinogenesis. In addition to discussion of addiction and computational studies, potential applications for health improvement are suggested.”

http://www.ncbi.nlm.nih.gov/pubmed/15654607

“Therefore, concentrations of butter flavoring vapors that can occur during the manufacture of foods are associated with epithelial injury in the nasal passages and pulmonary airways of rats.”

Toxicology And Applied Pharmacology • December 2002

Necrosis of nasal and airway epithelium in rats inhaling vapors of artificial butter flavoring

Hubbs AF1, Battelli LA, Goldsmith WT, Porter DW, Frazer D, Friend S,
Schwegler-Berry D, Mercer RR, Reynolds JS, Grote A, Castranova V, Kullman G,
Fedan JS, Dowdy J, Jones WG.

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Abstract

As the result of a high prevalence of fixed airways obstruction in workers at a microwave popcorn manufacturing plant, we examined the hypothesis that vapors of butter flavoring used in the manufacture of microwave popcorn and other foods can produce airway injury in rats. Rats were exposed to vapors liberated from heated butter flavoring. Rats were exposed for 6 h by inhalation and were necropsied 1 day after exposure. The exposure was found by GC-MS analysis to be a complex mixture of various organic gases with the major peaks consisting of diacetyl (2,3-butanedione), acetic acid, acetoin (3-hydroxy-2-butanone), butyric acid, acetoin dimers, 2-nonanone, and delta-alkyl lactones. Diacetyl was used as a marker of exposure concentration. In the lung, butter flavoring vapors containing 285-371 ppm diacetyl caused multifocal, necrotizing bronchitis, which was most consistently present in the mainstem bronchus. Alveoli were unaffected. Butter flavoring vapors containing 203-371 ppm diacetyl caused necrosuppurative rhinitis, which affected all four levels of the nose. Within the posterior two nasal levels (T3 and T4), necrosis and inflammation was principally localized to the nasopharyngeal duct. Control rats were unaffected. Therefore, concentrations of butter flavoring vapors that can occur during the manufacture of foods are associated with epithelial injury in the nasal passages and pulmonary airways of rats.

http://www.ncbi.nlm.nih.gov/pubmed/12490137

Japanese Journal On Cancer Research • September 1985

Potential initiating and promoting activities of diacetyl and glyoxal in rat stomach mucosa

Furihata C, Yoshida S, Matsushima T.

> “These results suggest that Diacetyl and Glyoxal have potential tumor-promoting activities and may also have initiating activities in carcinogenesis in the glandular stomach.”

Abstract

The potential initiating and promoting activities in the rat glandular stomach of the dicarbonyl compounds diacetyl (DA) and glyoxal (G), which are found in various heated foods, were studied. Administration of DA at doses of 300 to 1500 mg/kg body weight and of G at doses of 150 to 400 mg/kg body weight by gastric intubation to male F344 rats induced up to 100-fold increase in ornithine decarboxylase activity (formation of 195 pmol CO2/30 min/mg protein by DA and 302 pmol CO2/30 min/mg protein by G) with maxima after 16 hr. These treatments also induced a more than 10-fold increase in DNA synthesis (incorporation of 11,400 dpm of [3H]dThd/microgram DNA by DA and 15,100 dpm of [3H]dThd/microgram DNA by G) with maxima after 16 hr, and induced apparent unscheduled DNA synthesis in the pyloric mucosa of the stomach within 3 hr after administration. These results suggest that DA and G have potential tumor-promoting activities and may also have initiating activities in carcinogenesis in the glandular stomach.

http://www.ncbi.nlm.nih.gov/pubmed/3932277

CHAPTER TWENTY-ONE

'Natural Flavors'

The Peer Review

What's particularly alarming when you see a word like "artificial flavor" or even "natural flavor" on an ingredients label is that there's no way to know what it actually means. It could mean that one unnatural additive is included, or it could be a blend of hundreds of additives. Strawberry artificial flavor can contain nearly 50 chemical ingredients, for example.

Most people assume that a natural flavor describes something like strawberries, garlic, or chili pepper used to naturally season food. In reality, most natural flavors are created in a laboratory, just like artificial flavors. The only difference is that natural flavors must be sourced from a natural product, whereas artificial flavors do not. According to the Code of Federal Regulations:

"The term natural flavor or natural flavoring means the essential oil, oleoresin, essence or extractive, protein hydrolysate, distillate, or any product of roasting, heating or enzymolysis. These contain the flavoring constituents derived from a spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf or similar plant material, meat, seafood, poultry, eggs, dairy products, or fermentation products thereof, whose significant function in food is flavoring rather than nutritional."

In the end, natural flavors often bear little resemblance to the natural product from which they came. Many times, the resulting chemical may even be identical to those created synthetically to make artificial flavors, yet it will likely be more expensive. Some natural flavors even contain propylene glycol, a solvent, or the preservative BHA! Genetically engineered flavor enhancers can also be listed under the artificial flavor (or natural flavor) label.

One exception is certified organic natural flavors, which must meet more stringent guidelines and cannot contain synthetic or genetically engineered ingredients.

Little is available on "natural" flavors

Pediatrics • May 1993

The mystery ingredients: sweeteners, flavorings, dyes, and preservatives in analgesic/antipyretic, antihistamine/decongestant, cough and cold, antidiarrheal, and liquid theophylline preparations

Author information

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Abstract

OBJECTIVE

Pharmaceutical preparations may contain a variety of excipients ("inert ingredients"). These excipients are generally inactive; however, rare adverse effects caused by excipients have been reported. Information about the excipients in a particular preparation is not readily available.

METHODS

The information about sweeteners, flavorings, dyes, and preservatives for the chewable and liquid preparations of over-the-counter and prescription products of antidiarrhea, cough and cold, antihistamine/decongestant, analgesic/antipyretic, and liquid theophylline medications was collected.

RESULTS

"Information about excipients in 102 chewable and liquid preparations was compiled. An average preparation contained two sweeteners. Saccharin and sucrose were the most common sweeteners found--each was present in 52 preparations--followed by sorbitol, glucose, fructose, and others. For 36 of the 102 preparations, type of flavoring was not specified. In the remaining preparations, cherry was the most common flavoring, followed by vanilla and lemon. Twenty-one different dyes and coloring agents were used. Red dye No. 40 was the most common (42/102), followed by yellow No. 6 (27/102). Of the eight preservatives used, sodium benzoate and methylparabens were present in 42 and 27 of the preparations, respectively. Tables detailing these excipients and adverse effects reported are presented."

CONCLUSIONS

The tables should be helpful to physicians in selecting preparations containing different excipients when an adverse reaction occurs. The mandatory labeling of excipients in all pharmaceutical preparations is the only way that physicians and patients can be fully informed.

http://www.ncbi.nlm.nih.gov/pubmed/7682684

Pediatrics • March 1991

Sweeteners, flavorings, and dyes in antibiotic preparations

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Author information

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Abstract

Even though a variety of adverse effects caused by sweeteners, flavorings, and dyes in susceptible individuals have been reported, there is no good single reference with information about these substances in pediatric antimicrobials.

"Data on sweeteners, flavorings, and dyes in 91 antimicrobial preparations were collected. Sucrose was present in 74 (85%) of 87 preparations, followed by saccharin in 30 (34%) preparations. Mannitol, lactose, and sorbitol were each present in 7 preparations. None of the preparations were free of sweeteners. Thirty-four (37%) of 91 preparations did not specify the flavoring content. While cherry was the most common flavoring used, there were 25 other flavorings. Thirteen different dyes and coloring agents were used in these antimicrobials. Red dye no. 40 was present in 45% of preparations."

Tables detailing sweeteners, flavorings, and dyes in different groups of antimicrobials (amoxicillin, ampicillin, cephalosporins, erythromycin, penicillins, sulfonamides, and others) and adverse effects reported with these inert ingredients are presented. These tables should be helpful to physicians in selecting an antimicrobial containing a different sweetener and/or dye when an adverse reaction occurs.

http://www.ncbi.nlm.nih.gov/pubmed/2000275

CHAPTER TWENTY-TWO

Phosphates

The Peer Review

Phosphates have been implicated in Chronic Kidney Disease and a high phosphorous diet can cause disorders related to renal function, bone metabolism and vascular function. Excess phosphorous consumption from processed foods has been shown to be clearly associated with cardiovascular disease, osteoporosis, chronic bone disease and all cause mortality in the general, healthy population. Excess phosphorous also disrupts hormonal regulation of calcium and vitamin D. Research scientists have called for phosphorous content to be labeled in food while others have asked for its removal from processed foods completely. Best to avoid phosphorous and phosphate additives other than those that occur naturally in trace amounts in food. Phosphate additives are used primarily in low-cost foods. While we absorb a small percentage of food-bound phosphates, we absorb almost 100% of phosphates or polyphosphates contained in food additives.

Clinical Nutrition • February 2016

To reconsider (limit) the use of phosphate based food and beverages additives. A real need for health preservation

Author information

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http://www.ncbi.nlm.nih.gov/pubmed/26517950

“The extra-phosphate load from P-containing food and beverages remains the main concern of hidden phosphorus sources in chronic kidney disease patients.”

Journal Of Nephrology • April 2016

The extra-phosphate intestinal load from medications: is it a real concern?

Author information

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Abstract

BACKGROUND AND AIMS

Reduction of intestinal load of phosphorus is important for the prevention and treatment of chronic kidney disease (CKD)-mineral and bone disorder (MBD). However, this strategy is limited by patients’ poor adherence to dietary prescription and by the existence of hidden sources of phosphorus. In addition to food containing phosphate-based additives, it was recently claimed that medications may contribute to increase the load of phosphate (P), mainly present as an excipient. To identify medications containing P as an excipient, we performed a systematic screening of medications which could potentially be prescribed for chronic oral therapies in CKD patients.

METHODS

We examined 311 active pharmaceutical ingredients (APIs) and 3763 branded or generic medications, identified by the anatomical therapeutic chemical (ATC) international classification system.

RESULTS

Sixty APIs (19.3 %) included at least one medication containing P as an excipient. In total, 472 medications (12.5 %) listed P as an excipient. The prevalence of medications containing phosphate as an excipient was highest for oral antidiabetic medications (23.8 %), followed by antidepressant (19.2 %), antihypertensive (17.5 %) and gastro-intestinal tract (16.4 %) medications. All other classes showed a prevalence <10 %. Within each ATC class, the APIs at risk of containing phosphate were identified as well as the prevalence of both branded and generic medications. Calcium hydrogen phosphate was the most prevalent form (77.7 %) of phosphate as an excipient.

CONCLUSIONS

Our results suggest that the prevalence of phosphate-containing medications is quite low and it is possible to identify, within each drug category, the medications containing P as an excipient. Calcium phosphate, the most prevalent form, has a lower rate of intestinal absorption than sodium phosphate salts. We did not measure the actual P content, but existing data (measured or estimated) show that it is generally low, except for a few medications that can be easily identified. Thus, the extra-phosphate load from medications may be of concern only in special cases, which could be further limited when correct information and prescriptions are given. The extra-phosphate load from P-containing food and beverages remains the main concern of hidden phosphorus sources in CKD patients.

http://www.ncbi.nlm.nih.gov/pubmed/27084800

“A high phosphorus (HP) diet causes disorders of renal function, bone metabolism, and vascular function.”

PLoS One • May 2016

A High Phosphorus Diet Affects Lipid Metabolism in Rat Liver: A DNA Microarray Analysis

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Abstract

A high phosphorus (HP) diet causes disorders of renal function, bone metabolism, and vascular function. We previously demonstrated that DNA microarray analysis is an appropriate method to comprehensively evaluate the effects of a HP diet on kidney dysfunction such as calcification, fibrillization, and inflammation. We reported that type IIb sodium-dependent phosphate transporter is significantly up-regulated in this context. In the present study, we performed DNA microarray analysis to investigate the effects of a HP diet on the liver, which plays a pivotal role in energy metabolism. DNA microarray analysis was performed with total RNA isolated from the livers of rats fed a control diet (containing 0.3% phosphorus) or a HP diet (containing 1.2% phosphorus). Gene Ontology analysis of differentially expressed genes (DEGs) revealed that the HP diet induced down-regulation of genes involved in hepatic amino acid catabolism and lipogenesis, while genes related to fatty acid ß-oxidation process were up-regulated. Although genes related to fatty acid biosynthesis were down-regulated in HP diet-fed rats, genes important for the elongation and desaturation reactions of omega-3 and -6 fatty acids were up-regulated. Concentrations of hepatic arachidonic acid and eicosapentaenoic acid were increased in HP diet-fed rats. These essential fatty acids activate peroxisome proliferator-activated receptor alpha (PPARß), a transcription factor for fatty acid ß-oxidation. Evaluation of the upstream regulators of DEGs using Ingenuity Pathway Analysis indicated that PPARß was activated in the livers of HP diet-fed rats. Furthermore, the serum concentration of fibroblast growth factor 21, a hormone secreted from the liver that promotes fatty acid utilization in adipose tissue as a PPARß target gene, was higher ($p = 0.054$) in HP diet-fed rats than in control diet-fed rats. These data suggest that a HP diet enhances energy expenditure through the utilization of free fatty acids released via lipolysis of white adipose tissue.

Full text, graphs, charts and 40 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4871335/

National Chemical Biology • June 2016

A family of metal-dependent phosphatases implicated in metabolite damage-control

Author information

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Abstract

DUF89 family proteins occur widely in both prokaryotes and eukaryotes, but their functions are unknown. Here we define three DUF89 subfamilies (I, II, and III), with subfamily II being split into stand-alone proteins and proteins fused to pantothenate kinase (PanK). We demonstrated that DUF89 proteins have metal-dependent phosphatase activity against reactive phosphoesters or their damaged forms, notably sugar phosphates (subfamilies II and III), phosphopantetheine and its S-sulfonate or sulfonate (subfamily II-PanK fusions), and nucleotides (subfamily I). Genetic and comparative genomic data strongly associated DUF89 genes with phosphoester metabolism. The crystal structure of the yeast (Saccharomyces cerevisiae) subfamily III protein YMR027W revealed a novel phosphatase active site with fructose 6-phosphate and Mg2+ bound near conserved signature residues Asp254 and Asn255 that are critical for activity.

> “These findings indicate that DUF89 proteins are previously unrecognized hydrolases whose characteristic in vivo function is to limit potentially harmful buildups of normal or damaged phosphometabolites.”

http://www.ncbi.nlm.nih.gov/pubmed/27322068

“It is important to consider whether habitual high phosphorus intake adversely affects bone health, because phosphorus intake has been increasing, whereas calcium intake has been decreasing in dietary patterns. A higher total habitual dietary phosphorus intake has been associated with higher serum parathyroid hormone (PTH) and lower serum calcium concentrations in healthy individuals. Higher serum parathyroid hormone concentrations have been shown in those who consume foods with phosphorus additives. These findings suggest that long-term dietary phosphorus loads and long-term hyperphosphatemia may have important negative effects on bone health.”

Advances In Nutrition • January 2014

Increasing dietary phosphorus intake from food additives: potential for negative impact on bone health

Author information

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Abstract

It is important to consider whether habitual high phosphorus intake adversely affects bone health, because phosphorus intake has been increasing, whereas calcium intake has been decreasing in dietary patterns. A higher total habitual dietary phosphorus intake has been associated with higher serum parathyroid hormone (PTH) and lower serum calcium concentrations in healthy individuals. Higher serum PTH concentrations have been shown in those who consume foods with phosphorus additives. These findings suggest that long-term dietary phosphorus loads and long-term hyperphosphatemia may have important negative effects on bone health. In contrast, PTH concentrations did not increase as a result of high dietary phosphorus intake when phosphorus was provided with adequate amounts of calcium. Intake of foods with a ratio of calcium to phosphorus close to that found in dairy products led to positive effects on bone health. Several randomized controlled trials have shown positive relations between dairy intake and bone mineral density. In our loading test with a low-calcium, high-phosphorus lunch provided to healthy young men, serum PTH concentrations showed peaks at 1 and 6 h, and serum fibroblast growth factor 23 (FGF23) concentrations increased significantly at 8 h after the meal. In contrast, the high-calcium, high-phosphorus meal suppressed the second PTH and FGF23 elevations until 8 h after the meal. This implies that adequate dietary calcium intake is needed to overcome the interfering effects of high phosphorus intake on PTH and FGF23 secretion. FGF23 acts on the parathyroid gland to decrease PTH mRNA and PTH secretion in rats with normal kidney function. However, increased serum FGF23 is an early alteration of mineral metabolism in chronic kidney disease, causing secondary hyperthyroidism, and implying resistance of the parathyroid gland to the action of FGF23 in chronic kidney disease. These findings suggest that long-term high-phosphorus diets may impair bone health mediated by FGF23 resistance both in chronic kidney disease patients and in the healthy population.

Full text, graphs, charts and 61 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3884105/

Advances In Nutrition • January 2014

Phosphorus and the kidney: What is known and what is needed

Author information

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Abstract

"A major role of the kidneys is to maintain phosphorus homeostasis. High serum phosphorus has been linked to all-cause and cardiovascular mortality in chronic kidney disease (CKD) both before and after initiation of renal replacement therapy. Considering the clinical implications of uncontrolled hyperphosphatemia, maintenance of phosphorus concentrations within an optimum range is standard of care in this patient population. Recently, the epidemiologic associations between serum phosphorus and worse outcome have been extended to the general population. This becomes even more important in view of the increasing dietary phosphorus intake in the American diet due in large part to the greater consumption of foods processed with phosphate additives. A greater understanding of mechanisms and epidemiology of altered phosphorus metabolism and disease in CKD may help clarify the possible role of excess dietary phosphorus as a health risk factor in the general population."

http://www.ncbi.nlm.nih.gov/pubmed/24425728

American Journal Of Clinical Nutrition • February 2014

High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III

Author information

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Abstract

BACKGROUND

Elevated serum phosphorus is associated with all-cause mortality, but little is known about risk associated with dietary phosphorus intake.

OBJECTIVE

We investigated the association between phosphorus intake and mortality in a prospective cohort of healthy US adults (NHANES III; 1998-1994).

DESIGN

Study participants were 9686 nonpregnant adults aged 20-80 y without diabetes, cancer, or kidney or cardiovascular disease. Exposure to dietary phosphorus, which was assessed by using a 24-h dietary recall, was expressed as the absolute intake and phosphorus density (phosphorus intake divided by energy intake). All-cause and cardiovascular mortality was assessed through 31 December 2006.

RESULTS

Median phosphorus intake was 1166 mg/d (IQR: 823-1610 mg/d); median phosphorus density was 0.58 mg/kcal (0.48-0.70 mg/kcal). Individuals who consumed more phosphorus-dense diets were older, were less often African American, and led healthier lifestyles (smoking, physical activity, and Healthy Eating Index). In analyses adjusted for demographics, cardiovascular risk factors, kidney function, and energy intake, higher phosphorus intake was associated with higher all-cause mortality in individuals who consumed >1400 mg/d [adjusted HR (95% CI): 2.23 (1.09, 4.5) per 1-unit increase in ln(phosphorus intake); P = 0.03]. At <1400 mg/d, there was no association. A similar association was seen between higher phosphorus density and all-cause mortality at a phosphorus density amount >0.35 mg/kcal [adjusted HR (95% CI): 2.27 (1.19, 4.33) per 0.1-mg/kcal increase in phosphorus density; P = 0.01]. At <0.35 mg/kcal (approximately the fifth percentile), lower phosphorus density was associated with increased mortality risk. Phosphorus density was associated with cardiovascular mortality [adjusted HR (95% CI): 3.39 (1.43, 8.02) per 0.1 mg/kcal at >0.35 mg/kcal; P = 0.01], whereas no association was shown in analyses with phosphorus intake. Results were similar by subgroups of diet quality and in analyses adjusted for sodium and saturated fat intakes.

CONCLUSIONS

High phosphorus intake is associated with increased mortality in a healthy US population. Because of current patterns in phosphorus consumption in US adults, these findings may have important public health implications.

http://www.ncbi.nlm.nih.gov/pubmed/24225358

“High phosphorus intake is associated with increased mortality in a healthy US population.

Because of current patterns in phosphorus consumption in US adults, these findings may have important public health implications.”

“Excessive phosphorus consumption has now been shown to be clearly associated with cardiovascular disease, osteoporosis, and all-cause mortality in the general, healthy population.”

Integrated Medicine (Encinitas) • December 2014

Canaries in the Phosphate-Toxicity Coal Mines

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Abstract

Phosphorus is an essential mineral for cell structure and function but, when consumed in excess of the body’s requirements, has many adverse effects on metabolism and health. Recently published research has revealed that the average American consumes far more phosphorus than the recommended dietary allowance (RDA) (700 mg/d for adults). Some individuals’ daily phosphorus intake exceeds even an adult’s tolerable upper limit (4000 mg/d). Until now, understanding of the adverse effects caused by high phosphorus intake has come from patients with chronic kidney disease (CKD), in whom high levels of serum phosphates are strongly associated with increased cardiovascular and all-cause mortality. Due to their impaired renal function, CKD patients cannot clear excess phosphorus, for which reason they must avoid processed foods, virtually all of which are laden with phosphate-containing food additives. Recently, it has become apparent that CKD patients are our canaries in the phosphate-toxicity coal mines. Excessive phosphorus consumption has now been shown to be clearly associated with cardiovascular disease, osteoporosis, and all-cause mortality in the general, healthy population.

Full text, graphs, charts and 33 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4566440/

Seminars In Dialysis • January 2013

Contributions to total phosphorus intake: all sources considered

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Abstract

"High serum phosphorus is linked to poor health outcome and mortality in chronic kidney disease (CKD) patients before or after the initiation of dialysis. Dietary intake of phosphorus, a major determinant of serum phosphorus, seems to be systematically underestimated using the available software tools and generalized nutrient content databases. Several sources of dietary phosphorus including the addition of phosphorus ingredients in food processing, and phosphorus content of vitamin and mineral supplements and commonly used over-the-counter or prescription medications are not fully accounted for by the nutrient content databases and software programs in current clinical use or used in large population studies. In this review, we explore the many unknown sources of phosphorus in the food supply to identify all possible contributors to total phosphorus intake of Americans that have escaped inclusion in past intake estimates. Our goal is to help delineate areas for future interventions that will enable tighter control of dietary phosphorus intake, a critical factor to maintaining health and quality of life in CKD and dialysis patients."

http://www.ncbi.nlm.nih.gov/pubmed/23278245

“The increasing phosphorus intake due to the use of phosphorus-containing ingredients in processed food and the growing consumption of processed convenience and fast foods is an important factor that needs to be emphasized.”

Advances In Nutrition • September 2013

Dietary phosphorus excess: a risk factor in chronic bone, kidney, and cardiovascular disease?

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Abstract

There is growing evidence in the nephrology literature supporting the deleterious health effect of excess dietary phosphorus intake. This issue has largely escaped the attention of nutrition experts until this symposium, which raised the question of whether the same health concerns should be extended to the general population. The potential hazard of a high phosphorus intake in the healthy population is illustrated by findings from acute and epidemiologic studies. Acute studies in healthy young adults demonstrate that phosphorus intakes in excess of nutrient needs may significantly disrupt the hormonal regulation of phosphorus contributing to disordered mineral metabolism, vascular calcification, bone loss, and impaired kidney function. One of the hormonal factors acutely affected by dietary phosphorus loading is fibroblast growth factor-23, which may be a key factor responsible for many of the cardiovascular disease (CVD) complications of high phosphorus intake. Increasingly, large epidemiological studies suggest that mild elevations of serum phosphorus within the normal range are associated with CVD risk in healthy populations. Few population studies link high dietary phosphorus intake to mild changes in serum phosphorus due to study design issues specific to phosphorus and inaccurate nutrient composition databases. The increasing phosphorus intake due to the use of phosphorus-containing ingredients in processed food and the growing consumption of processed convenience and fast foods is an important factor that needs to be emphasized.

http://www.ncbi.nlm.nih.gov/pubmed/24038251

“Phosphorus intake in excess of the nutrient needs of healthy adults is thought to disrupt hormonal regulation of phosphorus (P), calcium (Ca), and vitamin D, contributing to impaired peak bone mass, bone resorption, and greater risk of fracture.”

Annals Of The New York Academy Of Science • October 2013

Is phosphorus intake that exceeds dietary requirements a risk factor in bone health?

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Abstract

Phosphorus intake in excess of the nutrient needs of healthy adults is thought to disrupt hormonal regulation of phosphorus (P), calcium (Ca), and vitamin D, contributing to impaired peak bone mass, bone resorption, and greater risk of fracture. Elevation of extracellular phosphorus due to excessive intake is thought to be the main stimulus disrupting phosphorus homeostasis in healthy individuals, as it is in renal disease even when intake is modest. If high serum phosphorus is the critical link to the effect of high phosphorus intake on bone health, the issue could be addressed through epidemiologic or dietary studies. However, several confounding factors, including problems estimating accurate phosphorus intake, the influence of a low dietary Ca:P ratio, the acidic nature of phosphorus, the rapid rate of absorption and greater phosphorus bioavailability from processed food such as cola drinks, and circadian fluctuation in serum phosphorus, make this question difficult to address using conventional study designs. These confounding factors are considered in this review, exploring whether phosphorus intake exceeding nutrient needs in healthy individuals disrupts phosphorus regulation and negatively affects bone accretion or loss. Specific attention is given to phosphorus intake from processed foods rich in phosphorus additives, which significantly contribute to phosphorus intake.

http://www.ncbi.nlm.nih.gov/pubmed/24472074

Deutsch Arztebl International • January 2012

Phosphate additives in food—a health risk

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Abstract

BACKGROUND

Hyperphosphatemia has been identified in the past decade as a strong predictor of mortality in advanced chronic kidney disease (CKD). For example, a study of patients in stage CKD 5 (with an annual mortality of about 20%) revealed that 12% of all deaths in this group were attributable to an elevated serum phosphate concentration. Recently, a high-normal serum phosphate concentration has also been found to be an independent predictor of cardiovascular events and mortality in the general population. Therefore, phosphate additives in food are a matter of concern, and their potential impact on health may well have been underappreciated.

METHODS

We reviewed pertinent literature retrieved by a selective search of the PubMed and EU databases (www.zusatzstoffe-online.de, www.codexalimentarius.de), with the search terms “phosphate additives” and “hyperphosphatemia.”

RESULTS

There is no need to lower the content of natural phosphate, i.e. organic esters, in food, because this type of phosphate is incompletely absorbed; restricting its intake might even lead to protein malnutrition. On the other hand, inorganic phosphate in food additives is effectively absorbed and can measurably elevate the serum phosphate concentration in patients with advanced CKD. Foods with added phosphate tend to be eaten by persons at the lower end of the socioeconomic scale, who consume more processed and “fast” food. The main pathophysiological effect of phosphate is vascular damage, e.g. endothelial dysfunction and vascular calcification. Aside from the quality of phosphate in the diet (which also requires attention), the quantity of phosphate consumed by patients with advanced renal failure should not exceed 1000 mg per day, according to the guidelines.

CONCLUSION

Prospective controlled trials are currently unavailable. In view of the high prevalence of CKD and the potential harm caused by phosphate additives to food, the public should be informed that added phosphate is damaging to health. Furthermore, calls for labeling the content of added phosphate in food are appropriate.

Full text, graphs, charts and 35 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278747/

“Prospective controlled trials are currently unavailable.

In view of the high prevalence of chronic kidney disease and the potential harm caused by phosphate additives to food, the public should be informed that added phosphate is damaging to health.

Furthermore, calls for labeling the content of added phosphate in food are appropriate.”

“Dietary intake of phosphorus (P) is derived largely from foods with high protein content or food additives and is an important determinant of P balance in patient with Chronic Kidney Disease.”

Clinical Calciumium • October 2012

Information about phosphorus additives and nutritional counseling

Author information

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Abstract

Hyperphosphatemia is a common disorder in patients with chronic kidney disease (CKD) , and may result in hyperparathyroidism and renal osteodystrophy. Hyperphosphatemia also may contribute to deterioration vascular calcification and increase mortality. Hence, correction and prevention of hyperphosphatemia is a main component of the management of CKD. This goal is usually approached both by administering phosphorus binders and by restricting dietary phosphorus (P) intake. Dietary intake of phosphorus (P) is derived largely from foods with high protein content or food additives and is an important determinant of P balance in patient with CKD. Food additives (PO4) can dramatically increase the amount of P consumed in the daily diet, especially because P is more readily absorbed in its inorganic form. In addition, information about the P content and type in prepared foods is often unavailable or misleading. Therefore, during dietary counseling of patients with CKD, we recommended that they consider both the absolute dietary P content and the P-to-protein ratio of foods and meals including food additives.

http://www.ncbi.nlm.nih.gov/pubmed/23023640

“The share of intestinal absorption (about 60% on average) is negligible for plant phosphorus (in the form of phytate), while it is maximal for phosphate or polyphosphates contained in food additives. The latter represent a dangerous extra load of phosphorus because they are poorly recognized by patients and widely used in modern nutrition, in particular in low-cost food.”

Giornale Italiano de Nefrologia • May 2011

The impact of known and unknown dietary components to phosphorus intake

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Abstract

The pathogenesis of CKD-MBD is multifactorial but the tendency towards phosphorus retention due to an excessive dietary intake for the residual renal function plays a central role. The dietary phosphorus is absorbed in the intestine as inorganic free phosphorus. The share of intestinal absorption (about 60% on average) is negligible for plant phosphorus (in the form of phytate), while it is maximal for phosphate or polyphosphates contained in food additives. The latter represent a dangerous extra load of phosphorus because they are poorly recognized by patients and widely used in modern nutrition, in particular in low-cost food. In a free mixed diet, the phosphorus content is directly related to that of proteins. It follows that protein-rich foods are the main source of phosphorus. This is a favorable condition for CKD patients in conservative therapy when a low-protein diet is implemented, while it represents a huge problem for dialysis patients, who need a high-protein diet. A simple and effective approach to reduce the load of dietary phosphorus without reducing protein intake is to educate patients to avoid foods high in phosphorus (cheese, egg yolk, nuts, etc.), and particularly those containing phosphorus additives. In addition, they should prefer boiling (resulting also in a decrease in sodium and potassium) to other methods of cooking. Counseling by a dietician is important for successful patient care. The dietician provides nutritional education, can help the patient with the choice of food, and may favor the adherence to dietary prescriptions, which is a crucial aspect in an integrated approach to CKD-MBD.

http://www.ncbi.nlm.nih.gov/pubmed/21626496

“Our results show that those foods which contain phosphate additives have a phosphorus content nearly 70% higher than the samples which did not contain additives. This creates a special concern because this extra amount of phosphorus is almost completely absorbed by the intestinal tract. These hidden phosphates worsen phosphate balance control and increase the need for phosphate binders and related costs.”

Journal Of Renal Nutrition • July 2011

Extra-phosphate load from food additives in commonly eaten foods: a real and insidious danger for renal patients

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Abstract

BACKGROUND

Restriction of dietary phosphorus is a major aspect of patient care in those with renal disease. Restriction of dietary phosphorus is necessary to control for phosphate balance during both conservative therapy and dialysis treatment. The extra amount of phosphorus which is consumed as a result of phosphate-containing food additives is a real challenge for patients with renal disease and for dieticians because it represents a “hidden” phosphate load. The objective of this study was to measure phosphorus content in foods, common protein sources in particular, and comprised both those which included a listing of phosphate additives and those which did not.

METHODS

Determinations of dry matter, nitrogen, total and soluble phosphate ions were carried out in 60 samples of foods, namely cooked ham, roast breast turkey, and roast breast chicken, of which, 30 were with declared phosphate additives and the other 30 similar items were without additives.

RESULTS

Total phosphorus (290 ± 40 mg/100 g vs. 185 ± 23 mg/100 g, $P < .001$) and soluble phosphorus (164 ± 25 mg/100 g vs. 100 ± 19 mg/100 g, $P < .001$) content were higher in products containing additives than in foods without additives. No difference was detected between the 2 groups regarding dry matter (27.2 ± 2.0 g/100 g vs. 26.7 ± 1.9 g/100 g) or total nitrogen (3.15 ± 0.40 g/100 g vs. 3.19 ± 0.40 g/100 g). Consequently, phosphorus intake per gram of protein was much greater in the foods containing phosphorus additives (15.0 ± 3.1 mg/g vs. 9.3 ± 0.7 mg/g, $P < .001$).

CONCLUSIONS

Our results show that those foods which contain phosphate additives have a phosphorus content nearly 70% higher than the samples which did not contain additives. This creates a special concern because this extra amount of phosphorus is almost completely absorbed by the intestinal tract. These hidden phosphates worsen phosphate balance control and increase the need for phosphate binders and related costs. Information and educational programs are essential to make patients with renal disease aware of the existence of foods with phosphate additives. Moreover, these facts highlight the need for national and international authorities to devote more attention to food labels which should clearly report the amount of natural or added phosphorus.

http://www.ncbi.nlm.nih.gov/pubmed/21055967

“In individuals with chronic kidney disease, high dietary phosphorus (P) burden may worsen hyperparathyroidism and renal osteodystrophy, promote vascular calcification and cardiovascular events, and increase mortality.”

Clinical Journal Of The American Society Of Nephrology • March 2010

Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease

Author information

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Abstract

In individuals with chronic kidney disease, high dietary phosphorus (P) burden may worsen hyperparathyroidism and renal osteodystrophy, promote vascular calcification and cardiovascular events, and increase mortality. In addition to the absolute amount of dietary P, its type (organic versus inorganic), source (animal versus plant derived), and ratio to dietary protein may be important. Organic P in such plant foods as seeds and legumes is less bioavailable because of limited gastrointestinal absorption of phytate-based P. Inorganic P is more readily absorbed by intestine, and its presence in processed, preserved, or enhanced foods or soft drinks that contain additives may be underreported and not distinguished from the less readily absorbed organic P in nutrient databases. Hence, P burden from food additives is disproportionately high relative to its dietary content as compared with natural sources that are derived from organic (animal and vegetable) food proteins. Observational and metabolic studies indicate nutritional and longevity benefits of higher protein intake in dialysis patients. This presents challenges to providing appropriate nutrition because protein and P intakes are closely correlated. During dietary counseling of patients with chronic kidney disease, the absolute dietary P content as well as the P-to-protein ratio in foods should be addressed. Foods with the least amount of inorganic P, low P-to-protein ratios, and adequate protein content that are consistent with acceptable palatability and enjoyment to the individual patient should be recommended along with appropriate prescription of P binders. Provision of in-center and monitored meals during hemodialysis treatment sessions in the dialysis clinic may facilitate the achievement of these goals.

http://www.ncbi.nlm.nih.gov/pubmed/20093346

“... compared with whites with the highest income, both blacks and whites with the lowest incomes had more than twice the likelihood of hyperphosphatemia in multivariable-adjusted analysis. In conclusion, low socioeconomic status associates with higher serum phosphate concentrations irrespective of race. Given the association between higher levels of serum phosphate and cardiovascular disease, further studies will need to determine whether excess serum phosphate may explain disparities in kidney disease outcomes among minority populations and the poor.”

Journal Of The American Society Of Nephrology • November 2010

Low socioeconomic status associates with higher serum phosphate irrespective of race

Author information

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Abstract

Hyperphosphatemia, which associates with adverse outcomes in CKD, is more common among blacks than whites for unclear reasons. Low socioeconomic status may explain this association because poverty both disproportionately affects racial and ethnic minorities and promotes excess intake of relatively inexpensive processed and fast foods enriched with highly absorbable phosphorus additives. We performed a cross-sectional analysis of race, socioeconomic status, and serum phosphate among 2879 participants in the Chronic Renal Insufficiency Cohort Study. Participants with the lowest incomes or who were unemployed had higher serum phosphate concentrations than participants with the highest incomes or who were employed ($P < 0.001$). Although we also observed differences in serum phosphate levels by race, income modified this relationship: Blacks had 0.11 to 0.13 mg/dl higher serum phosphate than whites in the highest income groups but there was no difference by race in the lowest income group. In addition, compared with whites with the highest income, both blacks and whites with the lowest incomes had more than twice the likelihood of hyperphosphatemia in multivariable-adjusted analysis. In conclusion, low socioeconomic status associates with higher serum phosphate concentrations irrespective of race. Given the association between higher levels of serum phosphate and cardiovascular disease, further studies will need to determine whether excess serum phosphate may explain disparities in kidney disease outcomes among minority populations and the poor.

Full text, graphs, charts and 44 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3014009/

“The results demonstrated inadequacies in bone related nutrients in our population as well that an increase in phosphorus intake is related to bone fractures.”

Nutrition Journal • January 2009

Nutrient intakes related to osteoporotic fractures in men and women—the Brazilian Osteoporosis Study (BRAZOS)

Author information

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Abstract

BACKGROUND

Adequate nutrition plays an important role in bone mass accrual and maintenance and has been demonstrated as a significant tool for the prevention of fractures in individuals with osteoporosis.

OBJECTIVE

The aim of the present study was to evaluate bone health-related nutrients intake and its association with osteoporotic fractures in a representative sample of 2344 individuals aged 40 years or older in Brazil.

METHODS

In a transversal population-based study, a total of 2420 individuals over 40 years old were evaluated from March to April 2006. Participants were men and women from all socio-economic classes and education levels living around the Brazilian territory Individuals responded a questionnaire including self reported fractures as well a 24-hour food recall. Nutrient intakes were evaluated by Nutrition Data System for Research software (NDSR, University of Minnesota, 2007). Low trauma fracture was defined as that resulting of a fall from standing height or less. Nutrient intakes adequacies were performed by using the DRI’s proposed values. Statistical analysis comprises Oneway ANCOVA adjusted by age and use of nutritional supplements and multiple logistic regression. SAS software was used for statistical analysis.

RESULTS

Fractures was reported by 13% of men and 15% of women. Women with fractures presented significantly higher calcium, phosphorus and magnesium intakes. However, in all regions and socio-economical levels mean intakes of bone related nutrients were below the recommended levels. It was demonstrated that for every 100 mg/phosphorus increase the risk of fractures by 9% (OR 1.09; IC95% 1.05-1.13, $p < 0.001$).

CONCLUSION

The results demonstrated inadequacies in bone related nutrients in our population as well that an increase in phosphorus intake is related to bone fractures.

http://www.ncbi.nlm.nih.gov/pubmed/19178745

“In conclusion, higher serum phosphorus levels, even within the normal range, may be a risk factor for coronary artery atherosclerosis in healthy young adults.”

Journal Of The American Society Of Nephrology • February 2009

Serum phosphorus levels associate with coronary atherosclerosis in young adults

Author information

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Abstract

Phosphorus levels correlate with atherosclerosis in both animal models and humans with advanced chronic kidney disease, but whether this relationship exists among individuals with normal kidney function is unknown. This study aimed to determine whether an association exists between phosphorus levels and coronary artery calcium levels in a community-based cohort of 3015 healthy young adults in the prospective Coronary Artery Risk Development in Young Adults (CARDIA) study. Phosphorus levels were measured at baseline, and presence of coronary artery calcium was assessed by computed tomography 15 yr later. Mean age at study inception was 25.2 yr, and the mean levels of phosphorus and calcium were 3.6 and 9.5 mg/dl, respectively. Only 0.2% of participants had estimated GFR <60 ml/min per 1.73 m(2). Phosphorus levels were associated with coronary artery calcium in unadjusted models. In multivariate models, however, phosphorus levels were significantly associated with the category of coronary artery calcium level. In conclusion, higher serum phosphorus levels, even within the normal range, may be a risk factor for coronary artery atherosclerosis in healthy young adults.

Full text, graphs, charts and 42 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2637043/

“Uncooked meat and poultry products that are enhanced may contain additives that increase phosphorus and potassium content by as much as almost two- and three-fold, respectively; this modification may not be discernible from inspection of the food label.”

Clinical Journal Of The American Society Of Nephrology • August 2009

Phosphorus and potassium content of enhanced meat and poultry products: implications for patients who receive dialysis

Author information

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Abstract

BACKGROUND AND OBJECTIVES

Uncooked meat and poultry products are commonly enhanced by food processors using phosphate salts. The addition of potassium and phosphorus to these foods has been recognized but not quantified.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS

We measured the phosphorus, potassium, and protein content of 36 uncooked meat and poultry products: Phosphorus using the Association of Analytical Communities (AOAC) official method 984.27, potassium using AOAC official method 985.01, and protein using AOAC official method 990.03.

RESULTS

Products that reported the use of additives had an average phosphate-protein ratio 28% higher than additive free products; the content ranged up to almost 100% higher. Potassium content in foods with additives varied widely; additive free products all contained <387 mg/100 g, whereas five of the 25 products with additives contained at least 692 mg/100 g (maximum 930 mg/100 g). Most but not all foods with phosphate and potassium additives reported the additives (unquantified) on the labeling; eight of 25 enhanced products did not list the additives. The results cannot be applied to other products. The composition of the food additives used by food processors may change over time.

CONCLUSIONS

Uncooked meat and poultry products that are enhanced may contain additives that increase phosphorus and potassium content by as much as almost two- and three-fold, respectively; this modification may not be discernible from inspection of the food label.

Full text with 17 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2723964/

“High total habitual dietary phosphorus intake affected serum parathyroid hormone unfavourably. Furthermore, phosphate additives may have more harmful effects on bone than other phosphorus sources, as indicated by higher mean serum parathyroid hormoneconcentration among participants who consumed phosphate-containing food additives. Because of the high dietary phosphorus intake and current upward trend in consumption of processed foods in Western countries, these findings may have important public health implications.”

Public Health And Nutrition • October 2009

Habitual high phosphorus intakes and foods with phosphate additives negatively affect serum parathyroid hormone concentration: a cross-sectional study on healthy premenopausal women

Author information

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Abstract

OBJECTIVE

Foods can contain natural phosphorus (NP) and phosphate-containing food additives (AP). The main objective of the present study was to investigate whether NP and AP of habitual diets differ in their effects on markers of Ca metabolism. We also investigated the impact of total habitual dietary P intake on markers of Ca metabolism.

DESIGN

Cross-sectional study. Fasting blood samples were collected and participants kept a 4 d food record, from which dietary intake of total P and the consumption of NP (milk and cheese, excluding processed cheese) and AP (processed cheese) sources were calculated. Participants were divided into groups according to their NP- and AP-containing food consumption and into quartiles according to their total P intake.

SETTING

Southern Finland

SUBJECTS

One hundred and forty-seven healthy premenopausal women aged 31-43 years.

RESULTS

Relative to the lowest total dietary P quartile, mean serum parathyroid hormone (S-PTH) concentration was higher (P = 0.048, analysis of covariance (ANCOVA)) and the mean serum ionized Ca concentration lower (P = 0.016, ANCOVA) in the highest P intake quartile. Mean S-PTH concentrations were higher among participants who consumed processed cheese (P = 0.027, ANCOVA) and less milk and other cheese than processed cheese (P = 0.030, ANCOVA).

CONCLUSIONS

High total habitual dietary P intake affected S-PTH unfavourably. Furthermore, phosphate additives may have more harmful effects on bone than other P sources, as indicated by higher mean S-PTH concentration among participants who consumed AP-containing foods. Because of the high dietary P intake and current upward trend in consumption of processed foods in Western countries, these findings may have important public health implications.

http://www.ncbi.nlm.nih.gov/pubmed/19216809

“The recommended dietary phosphorus intake is exceeded in the typical Western diet.”

Calcified Tissue International • April 2007

Acute effects of different phosphorus sources on calcium and bone metabolism in young women: a whole-foods approach

Author information

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Abstract

The recommended dietary phosphorus intake is exceeded in the typical Western diet. However, few studies have been conducted on the bioavailability and metabolic consequences of dietary phosphorus from different food sources. In this study, acute effects of dietary phosphorus from three different food sources and a phosphate supplement on calcium and bone metabolism were investigated. Sixteen healthy women aged 20-30 years were randomized to five controlled 24-hour study sessions, each subject serving as her own control. At the control session, calcium intake was ca. 250 mg and phosphorus intake ca. 500 mg. During the other four sessions, phosphorus intake was about 1,500 mg, 1,000 mg of which was obtained from meat, cheese, whole grains, or a phosphate supplement, respectively. The foods served were exactly the same during the phosphorus sessions and the control session; only phosphorus sources varied. Markers of calcium and bone metabolism were followed. Analysis of variance with repeated measures was used to compare the study sessions. Only the phosphate supplement increased serum parathyroid hormone (S-PTH) concentration compared with the control session ($P = 0.031$). Relative to the control session, meat increased markers of both bone formation ($P = 0.045$) and bone resorption ($P = 0.049$). Cheese decreased S-PTH ($P = 0.0001$) and bone resorption ($P = 0.008$). These data suggest that the metabolic response was different for different foods.

http://www.ncbi.nlm.nih.gov/pubmed/17401693

“Calcium and Phosphorus are both essential nutrients for bone and are known to affect one of the most important regulators of bone metabolism, parathyroid hormone (PTH). Too ample a Phosphorus intake, typical of Western diets, could be deleterious to bone through the increased parathyroid hormone secretion. Acutely high Phosphorus intake adversely affects bone metabolism by decreasing bone formation and increasing bone resorption, as indicated by the bone metabolism markers.”

British Journal Of Nutrition • September 2006

High phosphorus intakes acutely and negatively affect Ca and bone metabolism in a dose-dependent manner in healthy young females

Author information

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Abstract

Ca and P are both essential nutrients for bone and are known to affect one of the most important regulators of bone metabolism, parathyroid hormone (PTH). Too ample a P intake, typical of Western diets, could be deleterious to bone through the increased PTH secretion. Few controlled dose-response studies are available on the effects of high P intake in man. We studied the short-term effects of four P doses on Ca and bone metabolism in fourteen healthy women, 20-28 years of age, who were randomized to four controlled study days; thus each study subject served as her own control. P supplement doses of 0 (placebo), 250, 750 or 1500 mg were taken, divided into three doses during the study day. The meals served were exactly the same during each study day and provided 495 mg P and 250 mg Ca. The P doses affected the serum PTH (S-PTH) in a dose-dependent manner (P=0.0005). There was a decrease in serum ionized Ca concentration only in the highest P dose (P=0.004). The marker of bone formation, bone-specific alkaline phosphatase, decreased (P=0.05) and the bone resorption marker, N-terminal telopeptide of collagen type I, increased in response to the P doses (P=0.05). This controlled dose-response study showed that P has a dose-dependent effect on S-PTH and increases PTH secretion significantly when Ca intake is low. Acutely high P intake adversely affects bone metabolism by decreasing bone formation and increasing bone resorption, as indicated by the bone metabolism markers.

http://www.ncbi.nlm.nih.gov/pubmed/16925861

“We found a graded independent relation between higher levels of serum phosphate and the risk of death and cardiovascular events in people with prior myocardial infarction, most of whom had serum phosphate levels within the normal range.”

Circulation • October 2005

Relation between serum phosphate level and cardiovascular event rate in people with coronary disease

Author information

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Cholesterol And Recurrent Events Trial Investigators, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

Abstract

BACKGROUND

Higher levels of serum phosphate are associated with adverse cardiovascular outcomes, especially in the setting of overt hyperphosphatemia. Given the biological importance of phosphorus, it is plausible that higher levels of serum phosphate within the normal range may also be associated with adverse outcomes.

METHODS AND RESULTS

We performed a post hoc analysis of data from the Cholesterol And Recurrent Events (CARE) study. Baseline serum phosphate levels were measured in 4127 fasting participants who were randomized to receive pravastatin 40 mg daily or placebo and followed up for a median of 59.7 months. We used Cox proportional-hazards models to examine the association between serum phosphate and adverse clinical outcomes after adjustment for potential confounders. During nearly 60 months of follow-up, 375 participants died. A significant association was noted between baseline serum phosphate level and the age-, race-, and sex-adjusted risk of all-cause death (hazard ratio per 1 mg/dL, 1.27; 95% confidence interval, 1.02 to 1.58). After categorization based on baseline phosphate level (<2.5, 2.5 to 3.4, 3.5 to 3.9, and > or =4 mg/dL) and further adjustment, a graded independent relation between phosphate and death was observed (P for trend=0.03). For instance, participants with serum phosphate > or =3.5 mg/dL had an adjusted hazard ratio for death of 1.27 (95% confidence interval, 1.02 to 1.59) compared with those with serum phosphate of <3.5 mg/dL. Higher levels of serum phosphate were also associated with increased risk of new heart failure, myocardial infarction, and the composite of coronary death or nonfatal myocardial infarction, but not the risk of stroke.

CONCLUSIONS

We found a graded independent relation between higher levels of serum phosphate and the risk of death and cardiovascular events in people with prior myocardial infarction, most of whom had serum phosphate levels within the normal range. Given the ready availability and low cost of serum phosphate assays, this finding may prove clinically useful.

http://www.ncbi.nlm.nih.gov/pubmed/

Seminars In Dialysis • May 2003

Hidden sources of phosphorus in the typical American diet: does it matter in nephrology?

Uribarri J, Calvo MS.

Abstract

"Elevated serum phosphorus is a major, preventable etiologic factor associated with the increased cardiovascular morbidity and mortality of dialysis patients. An important determinant of serum phosphorus is the dietary intake of this mineral; this makes dietary restriction of phosphorus a cornerstone for the prevention and treatment of hyperphosphatemia. The average daily dietary intake of phosphorus is about 1550 mg for males and 1000 mg for females. In general, foods high in protein are also high in phosphorus. These figures, however, are changing as phosphates are currently being added to a large number of processed foods including meats, cheeses, dressings, beverages, and bakery products. As a result, and depending on the food choices, such additives may increase the phosphorus intake by as a much as 1 g/day. Moreover, nutrient composition tables usually do not include the phosphorus from these additives, resulting in an underestimate of the dietary intake of phosphorus in our patients. Our goal is to convey an understanding of the phosphorus content of the current American diet to better equip nephrologists in their attempt to control hyperphosphatemia."

http://www.ncbi.nlm.nih.gov/pubmed/12753675

Journal Of The American College Of Nutrition • August 2001

The institute of medicine's "dietary reference intake" for phosphorus: a critical perspective

By Leonard Sax
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Abstract

"Two questions relevant to the safety of phosphate additives have been raised in the literature: 1) Is the dietary ratio of calcium to phosphorus clinically significant in humans? Specifically, can a high-phosphorus, low-calcium diet cause hypocalcemia and/or secondary hyperparathyroidism in humans? 2) Does the growing use of phosphate-containing food additives increase the risk of low bone density and/or fracture in humans? In 1999, the Institute of Medicine published a monograph which addressed these two questions. This article critically reviews the findings and conclusions of the Institute of Medicine in the light of recent research."

http://www.ncbi.nlm.nih.gov/pubmed/11506054

Journal Of Nutrition • September 1993

Dietary phosphorus, calcium metabolism and bone

Author information

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Abstract

“Many American women consume diets high in phosphorus and low in calcium. Concern about this dietary pattern stems from studies that show high phosphorus, low calcium intake causes secondary hyperparathyroidism and bone loss in several animal models. Recent studies in young adults have shown that a high phosphorus, moderately low calcium intake results in mild secondary hyperparathyroidism that persisted over 4 wk. However, plasma concentrations of the active form of vitamin D did not change in these subjects, despite stimulatory changes in parathyroid hormone and serum ionized calcium. Studies in normal adult men have shown that dietary phosphorus at levels within the observed normal range of intake can finely regulate the renal production and serum concentration of 1,25-dihydroxycholecalciferol. Thus, prolonged high phosphorus intake may impair the usual homeostatic mechanisms that are evoked when dietary calcium is limited. The current dietary patterns of high phosphorus, low calcium consumption result in persistent changes in the calcium regulating hormones that are not conductive to optimizing peak bone mass or slowing the rate of bone loss.”

http://www.ncbi.nlm.nih.gov/pubmed/8360792

Journal Of Nutrition • January 1977

Physiological responses of human adults to foods containing phosphate additives

Bell RR, Draper HH, Tzeng DY, Shin HK, Schmidt GR.

Abstract

“An experiment was conducted to assess the physiological effects of a diet rich in foods cotaining phosphate additives. During a 4-week control period, eight adults were fed a balanced diet free of phosphate additives providing approximately 95 g protein 0.7 g Ca and 1.0 g P per day. During a subsequent 4-week period, food items containing phosphate additives were substituted for counterpart items devoid of added phosphates. This diet contained 0.7 g Ca and 2.1 g P per day. The introduction of foods containing phosphate additives was associated with intestinal distress, soft stools or mild diarrhea. These symptoms subsided in six subjects but occurred intermittently throughout the experimental period in the other two subjects. The high-phosphorus diet induced increases in serum phosphorus and urinary phosphorus and decreases in serum calcium and urinary calcium. Hydroxyproline excretion in the urine was increased and cyclic AMP excretion was elevated in six of the eight subjects. These changes are analogous to those seen in experimental animals fed high-phosphorus diets which were shown to be due to enhanced parathyroid activity (secondary hyperparathyroidism). The use of phosphate food additives is discussed with respect to their possible stimulating effect on adult bone resorption.”

http://www.ncbi.nlm.nih.gov/pubmed/189000

CHAPTER TWENTY-THREE

Sulfites

The Peer Review

Sulfites are substances that naturally occur in some foods and the human body. They are also used as regulated food additives.

Sulfites are used as a food preservative or enhancer. They may come in various forms, such as:

- Sulfur dioxide, which is not a sulfite, but a closely related chemical oxide
- Potassium bisulfite or potassium metabisulfite
- Sodium bisulfite, sodium metabisulfite or sodium sulfite

Sulfites occur naturally in all wines to some extent. Sulfites are commonly introduced to arrest fermentation at a desired time, and may also be added to wine as preservatives to prevent spoilage and oxidation at several stages of the winemaking process. Sulfur dioxide (SO2, sulfur with two atoms of oxygen) protects wine from not only oxidation, but also from bacteria. Without sulfites, grape juice would quickly turn to vinegar.

Organic wines are not necessarily sulfite-free, but generally have lower amounts and regulations stipulate lower maximum sulfite contents for these wines. In general, white wines contain more sulfites than red wines and sweeter wines contain more sulfites than drier ones.

In the United States, wines bottled after mid-1987 must have a label stating that they contain sulfites if they contain more than 10 parts per million.

In the European Union an equivalent regulation came into force in November 2005. In 2012, a new regulation for organic wines came into force.

Sulfites are often used as preservatives in dried fruits, preserved radish, and dried potato products. Most beers no longer contain sulfites, although some alcoholic ciders contain them. Although shrimp are sometimes treated with sulfites on fishing vessels, the chemical may not appear on the label. In 1986, the Food and Drug Administration in the United States banned the addition of sulfites to all fresh fruit and vegetables that are eaten raw.

Sulfites are counted among the top nine food allergens, but a reaction to sulfite is not a true allergy. Some people have positive skin allergy tests to sulfites indicating true (IgE-mediated) allergy. It may cause breathing difficulty within minutes after eating a food containing it. Asthmatics and possibly people with salicylate sensitivity (or aspirin sensitivity) are at an elevated risk for reaction to sulfites. Anaphylaxis and life-threatening reactions are rare. Other potential symptoms include sneezing, swelling of the throat, hives, and migraine.

In 1986, the U.S. Food and Drug Administration banned the use of sulfites as preservatives on foods intended to be eaten fresh (such as salad ingredients). This has contributed to the increased use of erythorbic acid and its salts as preservatives.

In the U.S., labeling regulations do not require products to indicate the presence of sulfites in foods unless it is added specifically as a preservative; however, many companies voluntarily label sulfite-containing foods. Sulfites used in food processing, but not specifically added as a preserva-

tive, are only required to be listed if there are more than 10 parts per million (ppm) in the finished product.

The products most likely to contain sulfites (fruits and alcoholic beverages less than 10ppm) do not require ingredients labels, so the presence of sulfites usually is undisclosed.

In Australia and New Zealand, sulfites must be declared in the statement of ingredients when present in packaged foods in concentrations of 10 mg/kg (ppm) or more as an ingredient; or as an ingredient of a compound ingredient; or as a food additive or component of a food additive; or as a processing aid or component of a processing aid.

The sulphites that can be added to foods in Canada are potassium bisulphite, potassium metabisulphite, sodium bisulphite, sodium dithionite, sodium metabisulphite, sodium sulphite, sulphur dioxide and sulphurous acid. These can also be declared using the common names sulfites, sulphites, sulfiting agents or sulphiting agents.

High sulfite content in the blood and urine of babies can be caused by molybdenum cofactor deficiency disease which leads to neurological damage and early death unless treated. Treatment, requiring daily injections, became available in 2009.

E numbers for sulfites as food additives are:

E150b	Caustic sulfite caramel
E150d	Sulfite ammonia caramel
E220	Sulfur dioxide
E221	Sodium sulfite
E222	Sodium bisulfite (sodium hydrogen sulfite)
E223	Sodium metabisulfite
E224	Potassium metabisulfite
E225	Potassium sulfite
E226	Calcium sulfite
E227	Calcium hydrogen sulfite (preservative)
E228	Potassium hydrogen sulfite

“Sulphite exposure accounted for 34%, 84% and 89% of the acceptable daily intakes in preschool children, females and males, respectively. In the high-intake scenario assuming that consumers always consume food products that contain additives and considering a kind of brand loyalty of consumers, the acceptable daily intake is exceeded for sulphites among adults (119 and 124%, respectively).”

Food Additive Contamination, Part A, Chemical Analysis, Control, Exposure And Risk Assessment • January 2012

Exposure assessment of food preservatives (sulphites, benzoic and sorbic acid) in Austria

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Abstract

An exposure assessment was performed to estimate the potential intake of preservatives in the Austrian population. Food consumption data of different population groups, such as preschool children aged 3-6 years, female and male adults aged 19-65 years were used for calculation. Levels of the preservatives in food were derived from analyses conducted from January 2007 to August 2010. Dietary intakes of the preservatives were estimated and compared to the respective acceptable daily intakes (ADIs). In the average-intake scenario, assuming that consumers randomly consume food products that do or do not contain food additives, estimated dietary intakes of all studied preservatives are well below the ADI for all population groups. Sulphite exposure accounted for 34%, 84% and 89% of the ADI in preschool children, females and males, respectively. The mean estimated daily intake of benzoic acid was 32% (preschool children), 31% (males) and 36% (females) of the ADI. Sorbic acid intakes correspond to 7% of the ADI in preschool children and 6% of the ADI in adults. In the high-intake scenario assuming that consumers always consume food products that contain additives and considering a kind of brand loyalty of consumers, the ADI is exceeded for sulphites among adults (119 and 124%, respectively). Major contributors to the total intake of sulphites were wine and dried fruits for adults. Mean estimated dietary intakes of benzoic acid exceeded the ADI in all population groups, 135% in preschool children, 124% in females and 118% of the ADI in males, respectively. Dietary intakes of sorbic acid are well below the ADI, accounting for a maximum of 30% of the ADI in preschool children. The highest contributors to benzoic and sorbic acid exposure were fish and fish products mainly caused by high consumption data of this large food group, including also mayonnaise-containing fish salads. Other important sources of sorbic acid were bread, buns and toast bread and fruit and vegetable juices.

http://www.ncbi.nlm.nih.gov/pubmed/22264192

“Exposure to sulphites has been reported to induce a range of adverse clinical effects in sensitive individuals, ranging from dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhoea to life-threatening anaphylactic and asthmatic reactions.”

Gastroenterology, Hepatology, From Bed To Bench • Winter 2012

Adverse reactions to the sulphite additives

Author information

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2. Adjunct Associate Professor, Lung Institute of Western Australia (Inc.), Centre for Asthma Allergy and Respiratory Research, The University of Western Australia, Perth, Australia

Abstract

Sulphites are widely used as preservative and antioxidant additives in the food and pharmaceutical industries. Exposure to sulphites has been reported to induce a range of adverse clinical effects in sensitive individuals, ranging from dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhoea to life-threatening anaphylactic and asthmatic reactions. Exposure to the sulphites arises mainly from the consumption of foods and drinks that contain these additives; however exposure may also occur through the use of pharmaceutical products, as well as in occupational settings. Most studies report a prevalence of sulphite sensitivity of 3 to 10% among asthmatic subjects who ingest these additives. However, the severity of these reactions varies, and steroid-dependent asthmatics, those with marked airway hyperresponsiveness, and children with chronic asthma, appear to be at greater risk. Although a number of potential mechanisms have been proposed, the precise mechanisms underlying sulphite sensitivity remain unclear.

Full text, graphs, charts and 72 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017440/

“While contact sensitivity to sulphite additives in topical medications is increasingly being recognized, skin reactions also occur after ingestion of or parenteral exposure to sulphites. Most studies report a 3-10% prevalence of sulphite sensitivity among asthmatic subjects following ingestion of these additives.”

Clinical And Experimental Allergy • November 2009

Clinical effects of sulphite additives

Author information

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Abstract

Sulphites are widely used as preservative and antioxidant additives in the food and pharmaceutical industries. Topical, oral or parenteral exposure to sulphites has been reported to induce a range of adverse clinical effects in sensitive individuals, ranging from dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhoea to life-threatening anaphylactic and asthmatic reactions. Exposure to the sulphites arises mainly from the consumption of foods and drinks that contain these additives; however, exposure may also occur through the use of pharmaceutical products, as well as in occupational settings. While contact sensitivity to sulphite additives in topical medications is increasingly being recognized, skin reactions also occur after ingestion of or parenteral exposure to sulphites. Most studies report a 3-10% prevalence of sulphite sensitivity among asthmatic subjects following ingestion of these additives. However, the severity of these reactions varies, and steroid-dependent asthmatics, those with marked airway hyperresponsiveness, and children with chronic asthma, appear to be at greater risk. In addition to episodic and acute symptoms, sulphites may also contribute to chronic skin and respiratory symptoms. To date, the mechanisms underlying sulphite sensitivity remain unclear, although a number of potential mechanisms have been proposed. Physicians should be aware of the range of clinical manifestations of sulphite sensitivity, as well as the potential sources of exposure. Minor modifications to diet or behaviour lead to excellent clinical outcomes for sulphite-sensitive individuals.

http://www.ncbi.nlm.nih.gov/pubmed/19775253

“The acceptable daily intake (ADI) could be exceeded for sulphites and BHT by a fraction of the population, in particular within children of 9-13 years old. Among all food additive-containing foods, the highest contributors were: soft drinks to benzoates intake, nuts and canned juices to sulphites intake, bread and biscuits to BHA intake and chewing gum to BHT intake.”

Regulatiry Toxicological Pharmacology • February 2007

Dietary exposure of children and teenagers to benzoates, sulphites, butylhydroxyanisol (BHA) and butylhydroxytoluen (BHT) in Beirut (Lebanon)

Author information

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Abstract

The acceptable daily intake (ADI) for a considered chemical is by definition the amount of that substance which can be ingested every day during the life time without appreciable health risk. The theoretical risk of exceeding the ADI for benzoates, sulphites, butylhydroxyanisol (BHA) and butylhydroxytoluen (BHT) has often been examined on the basis of worst case scenario. The aim of this paper is to assess the actual intake of the food additives listed above for a group of the Lebanese population (students aged between 9 and 18 years old) likely to be highly exposed to food additives through the consumption of processed foods. Dietary exposure was obtained by combining food consumption data with food additives levels determined by chemical analysis. Food products available in Lebanon and containing added benzoates, sulphites, BHA and BHT were identified. Overall 420 samples of foods and beverages were analysed. The determination of food additives residue levels was carried out according to the official methods adopted in “Lebanese Institute for agronomic research” (IRAL) on food as consumed. The acceptable daily intake (ADI) could be exceeded for sulphites and BHT by a fraction of the population, in particular within children of 9-13 years old. Among all food additive-containing foods, the highest contributors were: soft drinks to benzoates intake, nuts and canned juices to sulphites intake, bread and biscuits to BHA intake and chewing gum to BHT intake.

http://www.ncbi.nlm.nih.gov/pubmed/16996185

“Among all sulphite-containing foods, the highest contributors to the intake were dried fruit and wine, both ingested without further treatment. The analysis of specific consumption data confirmed the existence of a risk of exceeding the Acceptable Daily Intake related to sulphite residue levels in wine.”

Food Additive Contamination • December 2000

Dietary intake exposure to sulphites in Italy— analytical determination of sulphite-containing foods and their combination into standard meals for adults and children

Author information

Leclercq C1, Molinaro MG, Piccinelli R, Baldini M, Arcella D, Stacchini P.

National Institute for Food and Nutrition Research, Rome, Italy

Abstract

The theoretical risk of exceeding the Acceptable Daily Intake (ADI) for sulphites has mostly been examined on the basis of a worst-case scenario. In order to examine the real situation the determination of residue sulphite levels in ready-to-consume foods is required. The aim of this paper is to assess the actual sulphite content of diets obtained from a combination of realistic meals high in sulphite-containing foods. Food products available in Italy containing added sulphites were identified. Overall, 211 samples of foods and beverages (including 85 samples of wine) were collected. The determination of sulphite residues was carried out on the foods which were prepared according to normal domestic practice. It was shown that the diets obtained from these foods would lead to an intake of 23 mg/day in children and 50 mg/day in adults (both slightly above the ADI for respectively a 30 kg child and a 60 kg adult). Among all sulphite-containing foods, the highest contributors to the intake were dried fruit and wine, both ingested without further treatment. The analysis of specific consumption data confirmed the existence of a risk of exceeding the ADI related to sulphite residue levels in wine.

http://www.ncbi.nlm.nih.gov/pubmed/11271844

“These cases suggest that the amount of sulfite used was unnecessarily and dangerously high, and for one known sulfite-sensitive asthmatic, the use of the term “fresh” was misleading, resulting in near-fatal bronchospasm. Manufacturers should be careful to use only the minimum amount of sulfiting agent necessary.”

Home / Journal of Food Protection, Number 1 • January 1995

Clustered Outbreak of Adverse Reactions to a Salsa Containing High Levels of Sulfites

Author Information

Nagy, Stephen M.1; Teuber, Suzanne S.2; Loscutoff, Susan M.3; Murphy, Peter J.4

Abstract

Six patients came to our attention in the Sacramento, CA area who developed cough or asthma after the ingestion of one brand (Brand 1) of refrigerated Mexican-style salsa, labelled “fresh”. These patients had consumed other brands previously, not necessarily sulfited, but noted cough or asthma only in relation to consumption of this brand. Patients 1 and 2 developed reproducible severe cough and throat tightness after ingestion. Patients 3 and 4 developed status asthmaticus within minutes of ingesting salsa, requiring intubation and mechanical ventilation. Patients 5 and 6 experienced mild flares of their asthma after eating the salsa. The mean sulfite concentration of 6 containers of Brand 1 salsa was 1,803 ppm (range 1,630 to 1,920 ppm). Two other brands of salsa averaged 766 and 373 ppm sulfite, respectively. The manufacturer of Brand 1 salsa eliminated sulfites from their product after learning of the adverse reactions. These cases suggest that the amount of sulfite used was unnecessarily and dangerously high, and for one known sulfite-sensitive asthmatic, the use of the term “fresh” was misleading, resulting in near-fatal bronchospasm. Manufacturers should be careful to use only the minimum amount of sulfiting agent necessary.

http://www.ingentaconnect.com/content/iafp/jfp/1995/00000058/00000001/art00016

“Asthmatics who are steroid-dependent or who have a higher degree of airway hyperreactivity may be at greater risk of experiencing a reaction to sulfite-containing foods.”

Journal Of The American College Of Nutrition • June 1995

Sulfite sensitivity: significance in human health

By M.R. Lester

Abstract

Endogenous sulfite is generated as a consequence of the body’s normal processing of sulfur-containing amino acids. Sulfites occur as a consequence of fermentation and also occur naturally in a number of foods and beverages. As food additives, sulfiting agents were first used in 1664 and approved in the United States as long ago as the 1800s. With such long experience with their use, it is easy to understand why these substances have been regarded as safe. They are currently used for a variety of preservative properties, including controlling microbial growth, preventing browning and spoilage, and bleaching some foods. It is estimated that up to 500,000 (< .05% of the population) sulfite-sensitive individuals live in the United States. Sulfite sensitivity occurs most often in asthmatic adults--predominantly women; it is uncommonly reported in preschool children. Adverse reactions to sulfites in nonasthmatics are extremely rare. Asthmatics who are steroid-dependent or who have a higher degree of airway hyperreactivity may be at greater risk of experiencing a reaction to sulfite-containing foods. Even within this limited population, sulfite sensitivity reactions vary widely, ranging from no reaction to severe. The majority of reactions are mild. These manifestations may include dermatologic, respiratory, or gastrointestinal signs and symptoms. Severe non-specific signs and symptoms occur less commonly. Broncho-constriction is the most common sensitivity response in asthmatics. The precise mechanisms of the sensitivity responses have not been completely elucidated. Inhalation of sulfur dioxide (SO2) generated in the stomach following ingestion of sulfite-containing foods or beverages, a deficiency in a mitochondrial enzyme, and an IgE-mediated immune response have all been implicated.

http://www.ncbi.nlm.nih.gov/pubmed/8586770

Journal Of Toxicology, Clinical Toxicology • 1992

Review of parenteral sulfite reactions

Author information

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Abstract

“Sulfiting agents are commonly used in parenteral emergency drugs, including epinephrine, dexamethasone, dobutamine, dopamine, norepinephrine, phenylephrine, procainamide, and physostigmine. Published anaphylactic or asthmatic reactions have been associated with sulfited local anesthetics, gentamicin, metoclopramide, doxycycline, and vitamin B complex. The reactions differ from those caused by foods, in that they have a rapid onset, have no predilection for steroid-dependent asthmatics, and do not always coincide with a positive oral challenge. The mechanism is unknown, but may involve a dose-related reaction with disulfide bonds on sympathetic and parasympathetic receptor membranes. Patients with a history of positive oral challenge to 5-10 mg of sulfite may be at increased risk of developing a reaction to parenteral sulfites. Despite documentation of sensitivity, sulfites should not be withheld from patients experiencing a life-threatening emergency. Non-sulfited alternatives are often available, and should be used preferentially.”

http://www.ncbi.nlm.nih.gov/pubmed/1433430

“The authors point to the miscellaneous drugs containing sulfites, that are employed in asthmatics by different routes, i.e. parenteral, oral, inhalational and other local treatments. Heavy metabisulfite intake may also arise from daily alcohol consumption. Sulfite intolerance could contribute to the persistence of chronic inflammatory processes in bronchial asthma and therefore should be systematically investigated.”

La Review de Medecine Interne • January 1989

Severe complications related to metabisulfites

Author information

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Service de médecine “D”, Tour Drouet CHU de Brabois
Vandoeuvre-lès-Nancy, France

Abstract

Metabisulfite intolerance is encountered in 8 p. 100 of cases of extrinsic asthma and in 20 p. 100 of cases of the “aspirin triad” with nasosinusal polyposis, asthma and aspirin sensitivity. The possibility that anaphylactoid shock or acute severe asthma leading to status asthmaticus, might be related to sulfite sensitivity must be well known. Two case reports are set out. The first observation is that of a 35-year-old woman suffering from intrinsic asthma with alcohol intolerance, who developed status asthmaticus a few minutes after intravenous administration of Doxycycline associated with a metabisulfite preservative. The other 33-year-old patient presented with an acute bronchospasm in the course of a fiberoscopy using Lidocaine associated by mishap with epinephrine, as local anesthetic. The authors point to the miscellaneous drugs containing sulfites, that are employed in asthmatics by different routes, i.e. parenteral, oral, inhalational and other local treatments. Heavy metabisulfite intake may also arise from daily alcohol consumption. Sulfite intolerance could contribute to the persistence of chronic inflammatory processes in bronchial asthma and therefore should be systematically investigated.

http://www.ncbi.nlm.nih.gov/pubmed/2717827

CRC Critical Reviews In Toxicology • 1987

Sulfite hypersensitivity. A critical review

Gunnison AF, Jacobsen DW.

Abstract

“Sulfiting agents (sulfur dioxide and the sodium and potassium salts of bisulfite, sulfite, and metabisulfite) are widely used as preservatives in foods, beverages, and pharmaceuticals. Within the past 5 years, there have been numerous reports of adverse reactions to sulfiting agents. This review presents a comprehensive compilation and discussion of reports describing reactions to ingested, inhaled, and parenterally administered sulfite. Sulfite hypersensitivity is usually, but not exclusively, found within the chronic asthmatic population. Although there is some disagreement on its prevalence, a number of studies have indicated that 5 to 10% of all chronic asthmatics are sulfite hypersensitive. This review also describes respiratory sulfur dioxide sensitivity which essentially all asthmatics experience. Possible mechanisms of sulfite hypersensitivity and sulfur dioxide sensitivity are discussed in detail. Sulfite metabolism and the role of sulfite oxidase in the detoxification of exogenous sulfite are reviewed in relationship to the etiology of sulfite hypersensitivity.”

http://www.ncbi.nlm.nih.gov/pubmed/3556020

CHAPTER TWENTY-FOUR A

Sodium Benzoate

The Peer Review

Sodium benzoate is a widely used food preservative, with an E number of E211. It is the sodium salt of benzoic acid and exists in this form when dissolved in water. It can be produced by reacting sodium hydroxide with benzoic acid. Benzoic acid occurs naturally at low levels in cranberries, prunes, greengage plums, cinnamon, ripe cloves, and apples.

Sodium benzoate is bacteriostatic and fungistatic under acidic conditions. It is most widely used in acidic foods such as salad dressings (vinegar), carbonated drinks (carbonic acid), jams and fruit juices (citric acid), pickles (vinegar), and condiments. It is also used as a preservative in medicines and cosmetics. Concentration as a food preservative is limited by the FDA in the U.S. to 0.1% by weight. Sodium benzoate is also allowed as an animal food additive at up to 0.1%, according to AFCO's official publication.

Sodium benzoate is used as a treatment for urea cycle disorders due to its ability to bind amino acids. This leads to excretion of these amino acids and a decrease in ammonia levels. Recent research shows that sodium benzoate may be beneficial as an add-on therapy (1 gram/day) in schizophrenia. Total Positive and Negative Syndrome Scale scores dropped by 21% compared to placebo. Sodium benzoate is also used to treat hyperammonemia and Sodium benzoate has been shown to halt the progression of Parkinson's in mice.

The preserving mechanism starts with the absorption of benzoic acid into the cell. If the intracellular pH falls to 5 or lower, the anaerobic fermentation of glucose through phosphofructokinase decreases sharply which inhibits the growth and survival of microorganisms that cause food spoilage.

Sodium benzoate is produced by the neutralization of benzoic acid with sodium hydroxide. Sodium benzoate can also be prepared by adding benzoic acid to a hot concentrated solution of sodium carbonate until effervescence ceases. The solution is then evaporated, cooled and allowed to crystallize or evaporate to dryness, and then granulated.

In the United States, sodium benzoate is designated as generally recognized as safe (GRAS) by the Food and Drug Administration. The International Programme on Chemical Safety found no adverse effects in humans at doses of 647–825 mg/kg of body weight per day.

In combination with ascorbic acid (vitamin C, E300), sodium benzoate and potassium benzoate may form benzene, a known carcinogen. When tested by the FDA, most beverages that contained both ascorbic acid and benzoate had benzene levels that were below those considered dangerous for consumption by the World Health Organization (5 ppb). Most of the beverages that tested higher have been reformulated and subsequently tested below the safety limit. Heat, light and shelf life can increase the rate at which benzene is formed.

Research published in 2007 for the UK's Food Standards Agency (FSA) suggests that certain artificial colors, when paired with sodium benzoate, may be linked to hyperactive behavior. The results were inconsistent regarding sodium benzoate, so the FSA recommended further study. The Food Standards Agency concluded that the observed

increases in hyperactive behavior, if real, were more likely to be linked to the artificial colors than to sodium benzoate. The report's author, Jim Stevenson from Southampton University, said: "The results suggest that consumption of certain mixtures of artificial food colors and sodium benzoate preservative are associated with increases in hyperactive behavior in children. . . . Many other influences are at work but this is at least one a child can avoid."

Sodium benzoate may trigger or exacerbate symptoms or episodes of attention-deficit/hyperactivity disorder, or ADHD, according to the Mayo Clinic. The condition is most common in children but it can be present in adults as well, and affected individuals may be forgetful, have difficulty concentrating and following directions or display impulsiveness.

In response to consumer insistence on a more natural product, the Coca Cola Company is in the process of phasing sodium benzoate out of Diet Coke. The company has stated it plans to remove sodium benzoate from its other products—including Sprite, Fanta, and Oasis—as soon as a satisfactory alternative is discovered.

“Sodium benzoate had the mutagenic and cytotoxic toxicity in lymphocytes caused by micronucleus formation and chromosome break.”

BioMed Research International • Volume 2015 • Research Article

Effect of Sodium Benzoate Preservative on Micronucleus Induction, Chromosome Break, and Ala40Thr Superoxide Dismutase Gene Mutation in Lymphocytes

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Received 24 December 2014; Accepted 20 January 2015
Academic Editor: Davor Zeljezic

Abstract

Sodium benzoate is food preservative that inhibits microbial growth. The effects of sodium benzoate preservative on micronucleus induction, chromosome break, and Ala40Thr superoxide dismutase gene mutation in lymphocytes were studied. Sodium benzoate concentrations of 0.5, 1.0, 1.5, and 2.0 mg/mL were treated in lymphocyte cell line for 24 and 48 hrs, respectively. Micronucleus test, standard chromosome culture technique, PCR, and automated sequencing technique were done to detect micronucleus, chromosome break, and gene mutation. The results showed that, at 24- and 48-hour. incubation time, sodium benzoate concentrations of 1.0, 1.5, and 2.0 mg/mL increased micronucleus formation when comparing with the control group. At 24- and 48-hour. incubation time, sodium benzoate concentrations of 2.0 mg/mL increased chromosome break when comparing with the control group . Sodium benzoate did not cause Ala40Thr (GCGACG) in superoxide dismutase gene. Sodium benzoate had the mutagenic and cytotoxic toxicity in lymphocytes caused by micronucleus formation and chromosome break.

Full text, graphs, charts and 12 references

http://www.hindawi.com/journals/bmri/2015/103512/

“The performance of the sodium benzoate-treated rats was impaired in the elevated plus maze, an indicator of anxiety. Their riding time in fixed and accelerating speed rotarods was decreased, indicating motor impairment.”

Neurosciences (Riyadh) • January 2014

Sodium benzoate, a food preservative, induces anxiety and motor impairment in rats

Author information

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Abstract

OBJECTIVE

To investigate the behavioral characteristics, including anxiety and motor impairment, in sodium benzoate (NaB) treated rats.

METHODS

The study was carried out between July and September 2012 in the Laboratory Animal Center of Shiraz University of Medical Sciences, Shiraz, Iran. The rats were divided into 2 groups receiving distilled water and NaB (200mg/kg/day). All the animals received daily gavages for 4 weeks. At the end of the fourth week, anxiety, and motor function were assessed in elevated plus maze and rotarod test.

RESULTS

According to the results, NaB-treated rats spent less time in the open arm and had fewer entrances to the open arms in comparison with the control group ($p<0.04$). Also, the performance of the NaB-treated rats in fixed and accelerating speed rotarods was impaired, and the riding time (endurance) was lower than the control group ($p<0.01$).

CONCLUSION

The performance of the NaB-treated rats was impaired in the elevated plus maze, an indicator of anxiety. Their riding time in fixed and accelerating speed rotarods was decreased, indicating motor impairment.

http://www.ncbi.nlm.nih.gov/pubmed/24419445

“In conclusion, sodium benzoate may cause oxidative stress as food additive in human erythrocytes in vitro. Catechin or quercetin protected the erythrocytes against sodium benzoate-induced toxicity only at low concentrations of sodium benzoate. So, it appears that our findings provide evidence for the protection of erythrocytes from sodium benzoate that could be considered for further studies.”

Scientific World Journal • February 2014

Protective role of catechin and quercetin in sodium benzoate-induced lipid peroxidation and the antioxidant system in human erythrocytes in vitro

Author information
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Department of Biology, Faculty of Arts and Science, Bozok University, 66100 Divanli Yolu/Yozgat, Turkey

Abstract

The aim of this study was to evaluate the protective effect of catechin and quercetin in sodium benzoate- (SB-) induced oxidative stress in human erythrocytes in vitro. For this, the effects of SB (6.25, 12.5, 25, 50, and 100 µg/mL), catechin (10 µM), and quercetin (10 µM) on lipid peroxidation (LPO) and the activities of SOD, CAT, GPx, and GST were studied. Significantly higher LPO and lower activities of antioxidant enzymes were observed with the increasing concentrations of SB. Catechin or quercetin protected the erythrocytes against SB-induced toxicity only at low concentrations of SB. The presence of catechin or quercetin at 10 µM have no effect on SB-induced toxicity at high concentrations of SB (50 and 100 µg/mL). In conclusion, SB may cause oxidative stress as food additive in human erythrocytes in vitro. So, it appears that our findings provide evidence for the protection of erythrocytes from SB that could be considered for further studies.

Full text, graphs, charts and 45 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3943299/pdf/TSWJ2014-874824.pdf

“The sodium benzoate exposure with or without ascorbic acid treatment could alter the cerebellum. Yet, ascorbic acid could prevent the loss of some cells in the cerebellum.”

Saudi Medical Journal • December 2014

Stereological studies of the effects of sodium benzoate or ascorbic acid on rats cerebellum

Author information

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Histomorphometry and Stereology Research Center, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
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Abstract

OBJECTIVES

To evaluate the cerebellar structure in sodium benzoate (NaB) or ascorbic acid (AA) treated rats.

METHODS

This experimental study was conducted between May and September 2013 in the Laboratory Animal Center of Shiraz University of Medical Sciences, Shiraz, Iran. The rats received distilled either water, NaB (200mg/kg/day), AA (100mg/kg/day), or NaB+AA. The hemispheres were removed after 28 days and underwent quantitative study.

RESULTS

The total volume of the cerebellar hemisphere, its cortex, intracerebellar nuclei; the total number of the Purkinje, Bergman, granule, neurons, and glial cells of the molecular layer; and neurons and glial cells of the intracerebellar nuclei reduced by 21-52% in the NaB-treated rats compared with the distilled water group (p=0.004). The total number of the Purkinje, Bergman, Golgi, and granule cells was 29-45% higher in the AA-treated rats compared with the distilled water group (p=0.05). However, these measures reduced by 17-50% in the NaB+AA-treated rats compared with the distilled water group (p=0.004). The NaB+AA group did not induce any significant structural changes in comparison with the NaB group (p>0.05).

CONCLUSIONS

The NaB exposure with or without AA treatment could alter the cerebellum. Yet, AA could prevent the loss of some cells in the cerebellum.

http://www.ncbi.nlm.nih.gov/pubmed/25491215

“INTERVENTIONS: Six weeks of add-on treatment of 1 gram per day of sodium benzoate or placebo. Benzoate adjunctive therapy significantly improved a variety of symptom domains and neurocognition in patients with chronic schizophrenia.”

JAMA Psychiatry • December 2013

Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor

Author information
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Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan2Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan

Abstract

IMPORTANCE

In addition to dopaminergic hyperactivity, hypofunction of the N-methyl-d-aspartate receptor (NMDAR) has an important role in the pathophysiology of schizophrenia. Enhancing NMDAR-mediated neurotransmission is considered a novel treatment approach. To date, several trials on adjuvant NMDA-enhancing agents have revealed beneficial, but limited, efficacy for positive and negative symptoms and cognition. Another method to enhance NMDA function is to raise the levels of d-amino acids by blocking their metabolism. Sodium benzoate is a d-amino acid oxidase inhibitor.

OBJECTIVE

To examine the clinical and cognitive efficacy and safety of add-on treatment of sodium benzoate for schizophrenia.

DESIGN, SETTING, AND PARTICIPANTS

A randomized, double-blind, placebo-controlled trial in 2 major medical centers in Taiwan composed of 52 patients with chronic schizophrenia who had been stabilized with antipsychotic medications for 3 months or longer.

INTERVENTIONS

Six weeks of add-on treatment of 1 g/d of sodium benzoate or placebo.

MAIN OUTCOMES AND MEASURES

The primary outcome measure was the Positive and Negative Syndrome Scale (PANSS) total score. Clinical efficacy and adverse effects were assessed biweekly. Cognitive functions were measured before and after the add-on treatment.

RESULTS

Benzoate produced a 21% improvement in PANSS total score and large effect sizes (range, 1.16-1.69) in the PANSS total and subscales, Scales for the Assessment of Negative Symptoms-20 items, Global Assessment of Function, Quality of Life Scale and Clinical Global Impression and improvement in the neurocognition subtests as recommended by the National Institute of Mental Health’s Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative, including the domains of processing speed and visual learning. Benzoate was well tolerated without significant adverse effects.

CONCLUSIONS AND RELEVANCE

Benzoate adjunctive therapy significantly improved a variety of symptom domains and neurocognition in patients with chronic schizophrenia. The preliminary results show promise for d-amino acid oxidase inhibition as a novel approach for new drug development for schizophrenia.

TRIAL REGISTRATION

ClinicalTrials.gov NCT00960219.

http://www.ncbi.nlm.nih.gov/pubmed/24089054

“Decreased leptin release during the consumption of nutrition-derived food additives could decrease the amount of circulating leptin to which the central nervous system is exposed and may therefore contribute to an obesogenic environment.”

British Journal Of Nutrition • March 2012

Food additives such as sodium sulphite, sodium benzoate and curcumin inhibit leptin release in lipopolysaccharide-treated murine adipocytes in vitro

Author information
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Abstract

Obesity leads to the activation of pro-inflammatory pathways, resulting in a state of low-grade inflammation. Recently, several studies have shown that the exposure to lipopolysaccharide (LPS) could initiate and maintain a chronic state of low-grade inflammation in obese people. As the daily intake of food additives has increased substantially, the aim of the present study was to investigate a potential influence of food additives on the release of leptin, IL-6 and nitrite in the presence of LPS in murine adipocytes. Leptin, IL-6 and nitrite concentrations were analysed in the supernatants of murine 3T3-L1 adipocytes after co-incubation with LPS and the food preservatives, sodium sulphite (SS), sodium benzoate (SB) and the spice and colourant, curcumin, for 24 h. In addition, the kinetics of leptin secretion was analysed. A significant and dose-dependent decrease in leptin was observed after incubating the cells with SB and curcumin for 12 and 24 h, whereas SS decreased leptin concentrations after 24 h of treatment. Moreover, SS increased, while curcumin decreased LPS-stimulated secretion of IL-6, whereas SB had no such effect. None of the compounds that were investigated influenced nitrite production. The food additives SS, SB and curcumin affect the leptin release after co-incubation with LPS from cultured adipocytes in a dose- and time-dependent manner. Decreased leptin release during the consumption of nutrition-derived food additives could decrease the amount of circulating leptin to which the central nervous system is exposed and may therefore contribute to an obesogenic environment.

http://www.ncbi.nlm.nih.gov/pubmed/21801469

“Since alterations at the DNA level
such as DNA content and uncontrolled mitogenic stimulation
have been linked with chemical carcinogenesis, the results of the present study add information
on the toxicogenomic profile of the selected chemicals and may potentially lead to reconsideration
of the excessive use of nitrates aiming to protect public health.”

Acta Biologica Hungary • December 2012

DNA content alterations in Tetrahymena pyriformis macronucleus after exposure to food preservatives sodium nitrate and sodium benzoate

Author information
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Abstract

The toxicity, in terms of changes in the DNA content, of two food preservatives, sodium nitrate and sodium benzoate was studied on the protozoan Tetrahymena pyriformis using DNA image analysis technology. For this purpose, selected doses of both food additives were administered for 2 h to protozoa cultures and DNA image analysis of T. pyriformis nuclei was performed. The analysis was based on the measurement of the Mean Optical Density which represents the cellular DNA content. The results have shown that after exposure of the protozoan cultures to doses equivalent to ADI, a statistically significant increase in the macronuclear DNA content compared to the unexposed control samples was observed. The observed increase in the macronuclear DNA content is indicative of the stimulation of the mitotic process and the observed increase in MOD, accompanied by a stimulation of the protozoan proliferation activity is in consistence with this assumption. Since alterations at the DNA level such as DNA content and uncontrolled mitogenic stimulation have been linked with chemical carcinogenesis, the results of the present study add information on the toxicogenomic profile of the selected chemicals and may potentially lead to reconsideration of the excessive use of nitrates aiming to protect public health.

http://www.ncbi.nlm.nih.gov/pubmed/23134605

“Although sodium benzoate significantly increased DNA damage, potassium benzoate did not cause a significant increase in DNA damage. The present results indicate that sodium benzoate and potassium benzoate are clastogenic, mutagenic and cytotoxic to human lymphocytes in vitro.”

Food Chemical Toxicology • April 2011

The evaluation of the genotoxicity of two food preservatives: sodium benzoate and potassium benzoate

Author information

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Genetic Toxicology Laboratory, Department of Biology, Gazi University, Ankara, Turkey

Abstract

In this study, the genotoxic effects of sodium benzoate (SB) and potassium benzoate (PB) were investigated in cultured human peripheral lymphocytes using chromosomal aberrations (CA), sister chromatid exchange (SCE), and micronuclei (MN). The level of nuclear DNA damage of SB and PB were also evaluated using the comet assay. The lymphocytes were incubated with different concentrations of SB (6.25, 12.5, 25, 50, and 100 µg/ml) and PB (62.5, 125, 250, 500, and 1000 µg/ml). A significant increase was observed in CA, SCE, and MN, in almost all treatments compared to negative controls. SB and PB significantly decreased the mitotic index (MI) in all the treatments, compared to the negative controls. However, neither of the additives affected the replication index (RI). Although SB significantly increased DNA damage, PB did not cause a significant increase in DNA damage. The present results indicate that SB and PB are clastogenic, mutagenic and cytotoxic to human lymphocytes in vitro.

http://www.ncbi.nlm.nih.gov/pubmed/21130826

“The results of spectroscopic measurements indicated that sodium benzoate changed the internal microenvironment of trypsin and induced the alteration of the whole molecule, which were performed toxic effects on the organism.”

Spectrochima Acta Part A Molecular And Biomolecular Spectroscopy • December 2011

Interaction of sodium benzoate with trypsin by spectroscopic techniques

Author information

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School of Environmental Science and Engineering, Shandong University
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Abstract

The toxicity of sodium benzoate to trypsin was investigated by fluorescence spectroscopy, synchronous fluorescence spectroscopy, UV-visible absorption spectroscopy and circular dichroism (CD) spectroscopy under mimic physiological conditions. Sodium benzoate could unfold trypsin by decreasing the ß-sheet structure, which leads to more exposure of internal amino acid groups and the obvious intrinsic fluorescence quenching with the rising concentration of sodium benzoate. The results of spectroscopic measurements indicated that sodium benzoate changed the internal microenvironment of trypsin and induced the alteration of the whole molecule, which were performed toxic effects on the organism. Trypsin and sodium benzoate interacted with each other to produce a substance by van der Waals forces and hydrogen bond, the model of which was shown by AutoDock software.

http://www.ncbi.nlm.nih.gov/pubmed/21890401

“From the results, potassium sorbate is clearly seen to be genotoxic to the human peripheral blood lymphocytes in vitro.”

Toxicology In Vitro • April 2010

Does potassium sorbate induce genotoxic or mutagenic effects in lymphocytes?

Author information

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Abstract

The present study evaluates the genotoxic potential of potassium sorbate (PS) in cultured and isolated human lymphocytes. To assess the damage caused by PS in humans, we designed in vitro experiments by measuring chromosomal aberrations (CAs), sister-chromatid exchanges (SCEs), micronucleus (MN) and comet assays. Lymphocytes were treated with negative control (sterile distilled water), positive control (MMC for cultured lymphocytes, and H(2)O(2) for isolated lymphocytes) and four concentrations (125, 250, 500, and 1000 microg/ml) of PS. According to the results, PS treatment significantly increases the CAs (with or without gaps at 500 and 1000 microg/ml concentrations) and SCEs (at 250, 500, 1000 microg/ml for 24h and 125, 250, 500, 1000 microg/ml for 48h) compared with vehicle control. Following treatment of the isolated lymphocytes for 1h, significant PS-induced DNA strand breaks were observed, at all concentrations. However, PS failed to significantly affect the MN assay. On the contrary, PS does not cause cell cycle delay as noted by the non-significant decrease in the cytokinesis-block proliferation index (CBPI) and replicative index (RI). Only a slight decrease was observed in the mitotic index (MI) at the highest concentration for both treatment times. From the results, PS is clearly seen to be genotoxic to the human peripheral blood lymphocytes in vitro.

http://www.ncbi.nlm.nih.gov/pubmed/20036729

“This study may provide some important information for further elucidating the mechanism underlying sodium benzoate-induced developmental neurotoxicity.”

Birth Defects Research, Part B Developmental And Reproductive Toxicology • April 2009

Sodium benzoate exposure downregulates the expression of tyrosine hydroxylase and dopamine transporter in dopaminergic neurons in developing zebrafish

Author information
Chen Q1, Huang NN, Huang JT, Chen S, Fan J, Li C, Xie FK.
Department of Histology and Embryology, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, Guangdong Province, China

Abstract

BACKGROUND
Recent data have demonstrated that treatment with sodium benzoate (SB) leads to significant developmental defects in motor neuron axons and neuromuscular junctions in zebrafish larvae, thereby implying that SB can be neurotoxic. This study examined whether SB affects the development of dopaminergic neurons in the zebrafish brain.

METHODS
Zebrafish embryos were exposed to different concentrations of SB for various durations, during which the survival rates were recorded, the expression of tyrosine hydroxylase (TH) and dopamine transporter (DAT) in the neurons in the ventral diencephalon were detected by in situ hybridization and immunofluorescence, and the locomotor activity of larval zebrafish was measured.

RESULTS
The survival rates were significantly decreased with the increase of duration and dose of SB-treatment. Compared to untreated clutch mates (untreated controls), treatment with SB significantly downregulated expression of TH and DAT in neurons in the ventral diencephalon of 3-day post-fertilization (dpf) zebrafish embryos in a dose-dependent manner. Furthermore, there was a marked decrease in locomotor activity in zebrafish larvae at 6dpf in response to SB treatment.

CONCLUSIONS
The results suggest that SB exposure can cause significantly decreased survival rates of zebrafish embryos in a time- and dose-dependent manner and downregulated expression of TH and DAT in dopaminergic neurons in the zebrafish ventral diencephalon, which results in decreased locomotor activity of zebrafish larvae. This study may provide some important information for further elucidating the mechanism underlying SB-induced developmental neurotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/19294673

Sheng Wu Gong Cheng Xue Bao • August 2008

Analysis of sodium benzoate biotoxicity by atomic force microscope

Author information

Hu M1, Wang J, Cai J, Wu Y, Wang X.
Chemistry Department, Jinan University, Guangzhou 510632, China

Abstract

“Atomic force microscope (AFM) was used to study biotoxicity of food preservative sodium benzoate (SB) at the single cellular level. Lymphocyte morphology and membrane ultrastructure treated with SB at different concentrations and time were analyzed visually. As compared to the normal lymphocyte, the cell morphology and membrane was significantly changed and its ultrastructure was also complicated. After treated with SB, the Rp-v, Rq, Ra and Z values were changed. The statistical analysis of lymphocytes after treated with SB was studied, and discussed its mechanism.”

http://www.ncbi.nlm.nih.gov/pubmed/18998546

“Different abnormal mitotic figures were observed in all mitotic phases. Among these abnormalities were anaphase bridges, C-mitosis, micronuclei, lagging, stickiness, breaks and unequal distribution.”

Mutation Research • January 2007

Genotoxicity of five food preservatives tested on root tips of Allium cepa L.

Author information

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Abstract

The effects of the food preservatives **sodium benzoate (SB)**, boric acid (BA), citric acid (CA), potassium citrate (PC) and sodium citrate (SC) have been studied on root tips of Allium cepa L. Roots of A. cepa were treated with a series of concentrations, ranging from 20 to 100 ppm for 5, 10 and 20 h. The results indicate that these food preservatives reduced mitotic division in A. cepa compared with the respective control. Mitotic index values were generally decreased with increasing concentrations and longer treatment times. Additionally, variations in the percentage of mitotic stages were observed. The total percentage of aberrations generally increased with increasing concentrations of these chemicals and the longer period of treatment. Different abnormal mitotic figures were observed in all mitotic phases. Among these abnormalities were anaphase bridges, C-mitosis, micronuclei, lagging, stickiness, breaks and unequal distribution.

http://www.ncbi.nlm.nih.gov/pubmed/17005441

“On the basis of these observations, we suggest that sodium benzoate is able to induce neurotoxicity and nephrotoxicity of zebrafish larvae.”

Neurotoxicology And Teratology • September 2007

Treatment with sodium benzoate leads to malformation of zebrafish larvae

Author information

Tsay HJ1, Wang YH, Chen WL, Huang MY, Chen YH.
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Abstract

Sodium benzoate (SB) is a commonly used food preservative and anti-microbial agent in many foods from soup to cereals. However, little is known about the SB-induced toxicity and teratogenicity during early embryonic development. Here, we used zebrafish as a model to test the toxicity and teratogenicity because of their transparent eggs; therefore, the organogenesis of zebrafish embryos is easy to observe. After low dosages of SB (1-1000 ppm) treatment, the zebrafish embryos exhibited a 100% survival rate. As the exposure dosages increased, the survival rates decreased. No embryos survived after treatment with 2000 ppm SB. The 50% lethal dose (LD(50)) of zebrafish is found to be in the range of 1400-1500 ppm. Gut abnormalities, malformation of pronephros, defective hatching gland and edema in pericardial sac were observed after treatment with SB. Compared to untreated littermates (vehicle-treated control), SB-treated embryos exhibited significantly reduced tactile sensitivity frequencies of touch-induced movement (vehicle-treated control: 27.60+/-1.98 v.s. 1000 ppm SB: 7.89+/-5.28; N=30). Subtle changes are easily observed by staining with specific monoclonal antibodies F59, Znp1 and alpha6F to detect morphology changes in muscle fibers, motor axons and pronephros, respectively. Our data showed that the treatment of SB led to misalignment of muscle fibers, motor neuron innervations, excess acetyl-choline receptor cluster and defective pronephric tubes. On the basis of these observations, we suggest that sodium benzoate is able to induce neurotoxicity and nephrotoxicity of zebrafish larvae.

http://www.ncbi.nlm.nih.gov/pubmed/17644306

Toxicology • February 2005

Sodium benzoate attenuates D-serine induced nephrotoxicity in the rat

Author information

syngenta

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Abstract

D-Serine causes selective necrosis to the straight portion of the rat renal proximal tubules. The onset is rapid, occurring within 3-4 h and accompanied by proteinuria, glucosuria and aminoaciduria. The metabolism of D-serine by D-amino acid oxidase (D-AAO) may be involved in the mechanism of toxicity. D-AAO is localized within the peroxisomes of renal tubular epithelial cells, which is also the location of D-serine reabsorption. To address the role of D-AAO in D-serine-induced nephrotoxicity, we have examined the effect of sodium benzoate (SB) on the renal injury. SB has been shown to be a potent, competitive inhibitor of kidney D-AAO in vitro. Male Alderley Park rats were exposed to D-serine (500 mg/kg i.p.) 1 h after exposure to SB (125, 250, 500 or 750 mg/kg i.p.). Urine was collected for 0-6 h, then terminal plasma samples and kidneys were taken at 6.5 h. A second group of animals was given SB (500 mg/kg) followed by D-serine (500 mg/kg i.p.; 1 h later) and urine was collected after 0-6, 6-24 and 24-48 h. Terminal plasma samples and kidneys were taken at 48 h. 1H NMR spectroscopic analysis of urine, combined with principal component analysis, demonstrated that SB was able to prevent D-serine-induced perturbations to the urinary profile in a dose dependent manner. This was confirmed by measurement of plasma creatinine and urinary glucose and protein and histopathological examination of the kidneys. Assessment 48 h after D-serine administration revealed that nephrotoxicity was observed in animals pre-treated with SB (500 mg/kg) although the extent of injury was less pronounced than following D-serine alone. These results demonstrate that whilst prior exposure to SB prevents the initial onset of D-serine-induced nephrotoxicity, renal injury is still apparent at later time points. D-AAO activity in the kidney was decreased by 50% 1 h after dosing with SB suggesting that inhibition of this enzyme may be responsible for the observed protection.

http://www.ncbi.nlm.nih.gov/pubmed/15590120

Veterinary And Human Toxicology • March 2003

Assessing food additive toxicity using a cell model

Author information
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Department of Forensic Medicine and Toxicology
Medical School, University of Athens 75, M Asias Street, Goudi, Greece

Abstract

“Food additives are widely used for technological purposes and their presence is often substantial daily diet. They have also been accused for various toxic reactions in humans. The toxicity of the food color tartrazine, the preservatives sodium nitrate and sodium benzoate, and the antioxidant BHT, was studied using the protozoan Tetrahymenapyriformis as a toxicological model. The 4 food additives were added to Tetrahymena cultures and DNA content of the protozoan nuclei measured by an image analysis system. **These food additives caused a statistically significant increase in DNA content suggesting stimulation of the mitotic process. This system may contribute to the investigation of the cellular action of food additives, since mitogenic stimuli substantially alter susceptibility to chemical carcinogenesis.**”

http://www.ncbi.nlm.nih.gov/pubmed/12678300

International Journal Of Toxicology • January 2001

Final report on the safety assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate

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Abstract

Benzyl Alcohol is an aromatic alcohol used in a wide variety of cosmetic formulations as a fragrance component, preservative, solvent, and viscosity-decreasing agent. Benzoic Acid is an aromatic acid used in a wide variety of cosmetics as a pH adjuster and preservative. Sodium Benzoate is the sodium salt of Benzoic Acid used as a preservative, also in a wide range of cosmetic product types. Benzyl Alcohol is metabolized to Benzoic Acid, which reacts with glycine and excreted as hippuric acid in the human body. Acceptable daily intakes were established by the World Health Organization at 5 mg/kg for Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. Benzoic Acid and Sodium Benzoate are generally recognized as safe in foods according to the U.S. Food and Drug Administration. No adverse effects of Benzyl Alcohol were seen in chronic exposure animal studies using rats and mice. Effects of Benzoic Acid and Sodium Benzoate in chronic exposure animal studies were limited to reduced feed intake and reduced growth. Some differences between control and Benzyl Alcohol-treated populations were noted in one reproductive toxicity study using mice, but these were limited to lower maternal body weights and decreased mean litter weights. Another study also noted that fetal weight was decreased compared to controls, but a third study showed no differences between control and Benzyl Alcohol-treated groups. Benzoic Acid was associated with an increased number of resorptions and malformations in hamsters, but there were no reproductive or developmental toxicty findings in studies using mice and rats exposed to Sodium Benzoate, and, likewise, Benzoic Acid was negative in two rat studies. Genotoxicity tests for these ingredients were mostly negative, but there were some assays that were positive. Carcinogenicity studies, however, were negative. Clinical data indicated that these ingredients can produce nonimmunologic contact urticaria and nonimmunologic immediate contact reactions, characterized by the appearance of wheals, erythema, and pruritus. In one study, 5% Benzyl Alcohol elicited a reaction, and in another study, 2% Benzoic Acid did likewise. Benzyl Alcohol, however, was not a sensitizer at 10%, nor was Benzoic Acid a sensitizer at 2%. Recognizing that the nonimmunologic reactions are strictly cutaneous, likely involving a cholinergic mechanism, it was concluded that these ingredients could be used safely at concentrations up to 5%, but that manufacturers should consider the nonimmunologic phenomena when using these ingredients in cosmetic formulations designed for infants and children. Additionally, Benzyl Alcohol was considered safe up to 10% for use in hair dyes. The limited body exposure, the duration of use, and the frequency of use were considered in concluding that the nonimmunologic reactions would not be a concern. Because of the wide variety of product types in which these ingredients may be used, it is likely that inhalation may be a route of exposure. The available safety tests are not considered sufficient to support the safety of these ingredients in formulations where inhalation is a route of exposure. Inhalation toxicity data are needed to complete the safety assessment of these ingredients where inhalation can occur.

http://www.ncbi.nlm.nih.gov/pubmed/11766131

Toxicology Letters • August 1993

Short-term effect of sodium benzoate in F344 rats and B6C3F1 mice

Author information

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Tokyo Metropolitan Research Laboratory of Public Health, Japan

Abstract

“F344 rats and B6C3F1 mice of each sex were administered 0, 1.81, 2.09 or 2.40% (for rats) and 0, 2.08, 2.50 or 3.00% (for mice) of sodium benzoate in the diet for 10 days. In male rats of the 2.4% group, **relative liver and kidney weight, serum levels of albumin, total protein and gamma-glutamyl transpeptidase were significantly increased and enlarged hepatocytes with glassy cytoplasm were seen using light microscopy. In male mice of the 3.0% group, absolute liver weights and serum cholesterol and phospholipid levels were significantly increased, and enlargement, vacuolation and necrosis of hepatocytes were evident.**”

http://www.ncbi.nlm.nih.gov/pubmed/8212059

Tohoku Journal Of Experimental Medicine • May 1987

Cytotoxicities of sodium benzoate in primary culture of hepatocytes from adult rat liver

Oyanagi K, Kuniya Y, Nagao M, Tsuchiyama A, Nakao T.

Abstract

"The cytotoxicities of sodium benzoate was studied using primary culture of hepatocytes established from adult rat liver by a collagenase perfusion technique and maintained as a monolayer in serum-free culture medium. The activities of ornithine transcarbamylase (as a marker of mitochondria) and tyrosine aminotransferase (as a marker of cytosol) were clearly suppressed by sodium benzoate at concentration in excess of 500 micrograms/ml. Intracellular protein synthesis and DNA synthesis were also suppressed, and the suppression of DNA synthesis was observed even with a lower concentration of benzoate (100 micrograms/ml)."

Full text, graphs, charts and 6 references

https://www.jstage.jst.go.jp/article/tjem1920/152/1/152_1_47/_pdf

“The underlying mechanism of the altered bactericidal function of polymorphonuclear leukocytes treated with sodium benzoate appears to be a result of decreased uptake of S. aureus.”

Acta Pathologica, Microbiologica et Immunologica Scandinavica Section C • December 1983

Effect of sodium benzoate on polymorphonuclear leukocyte function

Johansen KS, Berger EM.

Abstract

Sodium benzoate is widely used as a food preservative and reputed to be a scavenger of hydroxyl radical (.OH). The effects of sodium benzoate on the function of polymorphonuclear leukocytes (PMN) stimulated by S. aureus or the chemical agent, phorbol myristate acetate (PMA) were examined in vitro using assays of chemiluminescence (CL), total bactericidal activity, intracellular recovery of bacteria, as well as release of lactate dehydrogenase (LDH), lysozyme and superoxide anion (O2(-)). Sodium benzoate decreased chemiluminescence, superoxide anion and lysozyme release by PMN stimulated with S. aureus but did not similarly affect these responses of PMN to the chemical agent, PMA. The ability of PMN to kill S. aureus was also impaired by sodium benzoate and associated with a reduced number of intracellular bacteria recovered after 90 minutes incubation. LDH release from PMN was not demonstrable at concentrations of sodium benzoate below 100 mM indicating that damage can not account for these findings. The underlying mechanism of the altered bactericidal function of PMN treated with sodium benzoate appears to be a result of decreased uptake of S. aureus.

http://www.ncbi.nlm.nih.gov/pubmed/6324535

“It was concluded that no evidence of carcinogenicity in rats from sodium benzoate was demonstrated.”

Journal Of Environmental And Pathological Toxicology • August 1980

Report of carcinogenesis bioassay of sodium benzoate in rats: absence of carcinogenicity of sodium benzoate in rats

Sodemoto Y, Enomoto M.

Abstract

The carcinogenicity of sodium benzoate was examined in Fischer 344 rats. Sodium benzoate was administered in the diet for 18 to 24 months at two dose levels; concentrations of 2% and 1% in the diet, which corresponded to the maximum tolerated dose (MTD) and 1/2 MTD as estimated from the data obtained by 6-week toxicity study. Fifty males and 52 females each were used per group. Controls consisted of 25 male rats and 43 female rats. No adverse clinical signs directly attributable to the compound were observed in treated animals. Differences in the average body weight, and mortality rates between treated and control groups were negligible. The results of the statistical test for dose-related trends were not significant ($p < 0.05$) Although a variety of tumors occurred among test and control rats of each sex, tumors appearing in treated rats were similar in type and number to those in controls. It was concluded that no evidence of carcinogenicity in rats from sodium benzoate was demonstrated.

http://www.ncbi.nlm.nih.gov/pubmed/7441132

Journal Of The National Cancer Institute • June 1977

Chromosome aberrations and sister chromatid exchanges in Chinese hamster cells exposed to various chemicals

Abe S, Sasaki M.

Abstract

"To evaluate its usefulness for detection of mutagenicity and oncogenicity of chemicals, the frequency of chromosome aberrations and sister chromatid exchanges (SCE) was examined in cultured Chinese hamster cells exposed to 33 kinds of chemical agents, including 2 aromatic hydrocarbons, 7 amine derivatives, 3 phenols, 6 carboxylic acid derivatives, 4 azo compounds, 7 heterocyclic compounds, and 4 other types of agents. Among them, 7 chemicals, including 5 known oncogens (N-n-butyl-N-nitrosourethan, N-methyl-N-nitrosourea, beta-propiolacton, methylazoxymethanol acetate, and propane sultone) and 2 non-oncogens (potassium sorbate and sodium benzoate) were inducers of aberrations and/or SCE, although the effective doses for the last two agents were considerably higher. The mutagenic activities estimated by chromosome aberrations were not necessarily the same for a given chemical when estimated by SCE. Slightly to moderately increased rates of SCE or aberrations were noticed among the other 26 chemicals. However, these values were usually without a clear dose relationship."

http://www.ncbi.nlm.nih.gov/pubmed/864744

“Compounds such as N-alkyl-N’-nitroguanidines, barbital, **sodium benzoate**, saccharin sodium, sodium nitrite, sodium nitrate and 4-aminoquinoline-1-oxide were positive in our chromosome tests ...”

Mutation Research • July 1977

Chromosome tests with 134 compounds on Chinese hamster cells in vitro—
a screening for chemical carcinogens

Ishidate M Jr, Odashima S.

Abstract

Chromosomal aberration tests in vitro were carried out on Chinese hamster cells grown in culture with various chemicals, including carcinogenic N-nitroso compounds and their related derivatives, food additives, medical drugs, pesticides and other chemicals commonly used in laboratories or industries. Sixty-three of the 134 chemicals gave negative results in our test system even with doses at which the cell growth was markedly inhibited. Nearly all compounds known to be mutagenic in bacteria were also positive in our tests. Both urethane and diethylstilbestrol were positive, even though they are known to be carcinogenic but not mutagenic in bacteria. Compounds such as N-alkyl-N’-nitroguanidines, barbital, sodium benzoate, saccharin sodium, sodium nitrite, sodium nitrate and 4-aminoquinoline-1-oxide were positive in our chromosome tests, but they have not been conclusively tested for their carcinogenicity.

http://www.ncbi.nlm.nih.gov/pubmed/876270

Journal Of General Physiology • May 1922

The effect of cocaine on the growth of lupinus albus
A contribution to the comparative pharmacology of animal and plant protoplasm

Author information

JOHNS HOPKINS

Macht DI1, Livingston MB.
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Abstract

“1. The effects of cocaine and its decomposition products were studied on the growth of the young roots of Lupinus albus. 2. The results obtained were compared with similar experiments on animal tissues. 3. It was found that, while cocaine is the most toxic of these compounds studied for animal tissues, it was of comparatively low toxicity in respect to its effect on the growth of roots. **On the other hand, sodium benzoate, being practically non-toxic for animals, was the most toxic of the compounds studied for the plant roots.**”

Full text with 9 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2140515/pdf/573.pdf

CHAPTER TWENTY-FOUR B

Sodium Benzoate As A Medically Prescribed Drug • Hepatic Encephalopathy

The Peer Review

Hepatic encephalopathy (HE) is the occurrence of confusion, altered level of consciousness, and coma as a result of liver failure. In the advanced stages it is called hepatic coma or coma hepaticum. It may ultimately lead to death.

It is caused by accumulation in the bloodstream of toxic substances that are normally removed by the liver. The diagnosis of hepatic encephalopathy requires the presence of impaired liver function and the exclusion of an alternative explanation for the symptoms. Blood tests (ammonia levels) may assist in the diagnosis. Attacks are often caused by another problem, such as infection or constipation.

Hepatic encephalopathy is reversible with treatment. This relies on suppressing the production of the toxic substances in the intestine and is most commonly done with the laxative lactulose or with non-absorbable antibiotics. In addition, the treatment of any underlying condition may improve the symptoms. In particular settings, such as acute liver failure, the onset of encephalopathy may indicate the need for a liver transplant.

SIGNS AND SYMPTOMS

The mildest form of hepatic encephalopathy is difficult to detect clinically, but may be demonstrated on neuropsychological testing. It is experienced as forgetfulness, mild confusion, and irritability. The first stage of hepatic encephalopathy is characterised by an inverted sleep-wake pattern (sleeping by day, being awake at night). The second stage is marked by lethargy and personality changes. The third stage is marked by worsened confusion. The fourth stage is marked by a progression to coma.

More severe forms of hepatic encephalopathy lead to a worsening level of consciousness, from lethargy to somnolence and eventually coma. In the intermediate stages, a characteristic jerking movement of the limbs is observed (asterixis, "liver flap" due to its flapping character); this disappears as the somnolence worsens. There is disorientation and amnesia, and uninhibited behaviour may occur. In the third stage, neurological examination may reveal clonus and positive Babinski sign. Coma and seizures represent the most advanced stage; cerebral oedema (swelling of the brain tissue) leads to death.

Encephalopathy often occurs together with other symptoms and signs of liver failure. These may include jaundice (yellow discolouration of the skin and the whites of the eyes), ascites (fluid accumulation in the abdominal cavity), and peripheral edema (swelling of the legs due to fluid build-up in the skin). The tendon reflexes may be exaggerated, and the plantar reflex may be abnormal, namely extending rather than flexing (Babinski's sign) in severe encephalopathy. A particular smell (foetor hepaticus) may be detected.

CAUSES

In a small proportion of cases, the encephalopathy is caused directly by liver failure; this is more likely in acute liver failure. More commonly, especially in chronic liver disease, hepatic encephalopathy is caused or aggravated by an additional cause, and identifying these causes can be important to treat the episode effectively.

Hepatic encephalopathy may also occur after the creation of a transjugular intrahepatic portosystemic shunt (TIPSS). This is used in the treatment of refractory ascites, bleeding from oesophageal varices and hepatorenal syndrome.[5][6] TIPSS-related encephalopathy occurs in about 30% of cases, with the risk being higher in those with previous episodes of encephalopathy, higher age, female sex and liver disease due to causes other than alcohol.

There are various explanations why liver dysfunction or portosystemic shunting might lead to encephalopathy. In healthy subjects, nitrogen-containing compounds from the intestine, generated by gut bacteria from food, are transported by the portal vein to the liver, where 80–90%

are metabolised through the urea cycle and/or excreted immediately. This process is impaired in all subtypes of hepatic encephalopathy, either because the hepatocytes (liver cells) are incapable of metabolising the waste products or because portal venous blood bypasses the liver through collateral circulation or a medically constructed shunt. Nitrogenous waste products accumulate in the systemic circulation (hence the older term "portosystemic encephalopathy"). The most important waste product is ammonia (NH3). This small molecule crosses the blood–brain barrier and is absorbed and metabolised by the astrocytes, a population of cells in the brain that constitutes 30% of the cerebral cortex. Astrocytes use ammonia when synthesising glutamine from glutamate. The increased levels of glutamine lead to an increase in osmotic pressure in the astrocytes, which become swollen. There is increased activity of the inhibitory γ-aminobutyric acid (GABA) system, and the energy supply to other brain cells is decreased. This can be thought of as an example of brain oedema of the "cytotoxic" type.

Despite numerous studies demonstrating the central role of ammonia, ammonia levels don't always correlate with the severity of the encephalopathy; it is suspected that this means that more ammonia has already been absorbed into the brain in those with severe symptoms whose serum levels are relatively low.

Other waste products implicated in hepatic encephalopathy include mercaptans (substances containing a thiol group), short-chain fatty acids and phenol.

Numerous other abnormalities have been described in hepatic encephalopathy, although their relative contribution to the disease state is uncertain. Loss of glutamate transporter gene expression (especially EAAT 2) has been attributed to acute liver failure. Benzodiazepine-like compounds have been detected at increased levels as well as abnormalities in the GABA neurotransmission system. An imbalance between aromatic amino acids (phenylalanine, tryptophan and tyrosine) and branched-chain amino acids (leucine, isoleucine and valine) has been described; this would lead to the generation of false neurotransmitters (such octopamine and 2-hydroxyphenethylamine). Dysregulation of the serotonin system, too, has been reported. Depletion of zinc and accumulation of manganese may play a role. Inflammation elsewhere in the body may precipitate encephalopathy through the action of cytokines and bacterial lipopolysaccharide on astrocytes.

Gastroenterology And Hepatology NY • February 2016

Contemporary Understanding and Management of Overt and Covert Hepatic Encephalopathy

Author information

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Dr NeSmith is a gastroenterology fellow and Dr Ahn is an associate professor of medicine and director of clinical hepatology at Oregon Health & Science University in Portland, Oregon. Dr Flamm is a professor of medicine and chief of the liver transplantation program at Northwestern University Feinberg School of Medicine in Chicago, Illinois

Abstract

“Hepatic encephalopathy (HE) is a major complication of liver disease that leads to significant morbidity and mortality. Caring for hospitalized patients with HE is becoming more complex, and the economic burden of HE continues to rise. Defining and diagnosing HE, particularly covert HE (CHE), remain challenging. In this article, we review new tools and those currently under development for the diagnosis of CHE and the latest advances in the acute and long-term management of overt HE (OHE) and CHE. In particular, we review the latest data on the use of lactulose and rifaximin for treatment of OHE and summarize the data on adjunctive agents such as **sodium benzoate** and probiotics.”

Full text, graphs, charts and 47 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4865778/pdf/GH-12-91.pdf

Seminars In Liver Disease • February 2016

Hepatic Encephalopathy: Pharmacological Therapies Targeting Ammonia

Author information

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Annette C. and Harold C. Simmons Transplant Institute, Baylor University Medical Center, Dallas, Texas
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Abstract

“Hepatic encephalopathy (HE) is a major complication in patients with decompensated cirrhosis, leading to higher readmission rates causing a profound burden of disease and considerable health care costs. Because ammonia is thought to play a crucial role in the pathogenesis of HE, therapies directed at reducing ammonia levels are now being aggressively developed. Ammonia scavengers such as AST-120 (spherical carbon adsorbent), glycerol phenylbutyrate, sodium phenylacetate or **sodium benzoate**, and ornithine phenylacetate have been used to improve HE symptoms. A new approach, bowel cleansing with polyethylene glycol 3350, appears to be a promising therapy, with a recent study demonstrating a more rapid improvement in overt HE (at 24 hours after treatment) than lactulose. Extracorporeal devices, although now used primarily in research settings, have also been utilized in patients with refractory HE, but are not approved for clinical management.”

http://www.ncbi.nlm.nih.gov/pubmed/26870932

Advanced Drug Delivery Reviews • August 2015

Recent advances in the treatment of hyperammonemia

Author information

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Abstract

Ammonia is a neurotoxic agent that is primarily generated in the intestine and detoxified in the liver. Toxic increases in systemic ammonia levels predominantly result from an inherited or acquired impairment in hepatic detoxification and lead to potentially life-threatening neuropsychiatric symptoms. Inborn deficiencies in ammonia detoxification mainly affect the urea cycle, an endogenous metabolic removal system in the liver. Hepatic encephalopathy, on the other hand, is a hyperammonemia-related complication secondary to acquired liver function impairment. A range of therapeutic options is available to target either ammonia generation and absorption or ammonia removal. Therapies for hepatic encephalopathy decrease intestinal ammonia production and uptake. Treatments for urea cycle disorders eliminate ammoniagenic amino acids through metabolic transformation, preventing ammonia generation. Therapeutic approaches removing ammonia activate the urea cycle or the second essential endogenous ammonia detoxification system, glutamine synthesis. Recent advances in treating hyperammonemia include using synergistic combination treatments, broadening the indication of orphan drugs, and developing novel approaches to regenerate functional liver tissue. This manuscript reviews the various pharmacological treatments of hyperammonemia and focuses on biopharmaceutical and drug delivery issues.

http://www.ncbi.nlm.nih.gov/pubmed/25895618

“Sodium benzoate is an inexpensive adjunctive agent that can be used in addition to lactulose and rifaximin and may provide an option for some select patients with refractory HE who have failed to respond to standard therapies or who cannot afford them. Although sodium benzoate does not share the same adverse effect profiles of standard therapies for HE, its efficacy has not been well established. Given the significant dose-dependent sodium content of this therapy, it may not be appropriate for patients with significant fluid retention or kidney dysfunction.”

Gastroenterology And Hepatology NY • April 2013

Sodium benzoate for treatment of hepatic encephalopathy

Author information

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and Abdominal Transplantation in the Division of GI Hepatology at the
University of California San Diego in San Diego, California

Abstract

Hepatic encephalopathy (HE) is a serious but usually reversible neuropsychiatric complication of cirrhosis, inborn errors of metabolism involving disorders of the urea cycle, and noncirrhotic portosystemic shunting that most commonly arises from a transjugular intrahepatic portosystemic shunting procedure. Symptoms can include alterations in cognitive function, neuromuscular activity, and consciousness, as well as sleep disorders and mood changes. HE is associated with significant morbidity and mortality and, if not properly treated, will lead to increased hospital admissions and healthcare costs. Although the standard therapies of lactulose and rifaximin (Xifaxan, Salix) are effective for most patients, these drugs may be associated with significant adverse effects and expense and, in some patients, inadequate therapeutic response. A need for adjunctive therapies exists. Drugs that target serum and tissue ammonia metabolism and elimination may be important adjuncts to drugs that reduce ammonia production and absorption from the gastrointestinal tract for patients with severe or persistent overt symptoms of HE. Sodium benzoate is an inexpensive adjunctive agent that can be used in addition to lactulose and rifaximin and may provide an option for some select patients with refractory HE who have failed to respond to standard therapies or who cannot afford them. Although sodium benzoate does not share the same adverse effect profiles of standard therapies for HE, its efficacy has not been well established. Given the significant dose-dependent sodium content of this therapy, it may not be appropriate for patients with significant fluid retention or kidney dysfunction.

http://www.ncbi.nlm.nih.gov/pubmed/24711766

Therapies In Clinical Risk Managment • June 2009

Current trends in the treatment of hepatic encephalopathy

Author information
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Abstract

“Hepatic encephalopathy (HE) is a common reversible neuropsychiatric syndrome associated with chronic and acute liver dysfunction and significant morbidity and mortality. Although a clear pathogenesis is yet to be determined, elevated ammonia in the serum and central nervous system are the mainstay for pathogenesis and treatment. Management includes early diagnosis and prompt treatment of precipitating factors (infection, gastrointestinal bleeding, electrolyte disturbances, hepatocellular carcinoma, dehydration, hypotension, and use of benzodiazepines, psychoactive drugs, and/or alcohol). Clinical trials have established the efficacy of lactulose and lactitol enemas in the treatment of acute hepatic encephalopathy. Extensive clinical experience has demonstrated the efficacy of oral lactulose and lactitol with the goal of two to three soft bowel movements a day for the treatment of chronic HE. However, lactulose and lactitol have significant gastrointestinal side effects. For patients unable to tolerate lactulose or lactitol or who still have persistent chronic HE with lactulose or lactitol, neomycin, metronidazole and rifaximin are second-line agents. More recent data supports the benefits of rifaximin used solely and as an additional agent with fewer side effects than neomycin or metronidazole. Newer therapies being investigated in humans with clinical promise include nitazoxanide, the molecular adsorbent recirculating system (MARS), L-ornithine phenylacetate, **sodium benzoate**, and/or sodium phenylacetate and Kremezin((R)) (AST-120).”

Full text, graphs, charts and 71 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2724191/pdf/tcrm-5-617.pdf

Journal Of Inherited Metabolic Disease • March 2000

Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia

Author information

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Abstract

“Intravenous sodium benzoate and sodium phenylacetate have been used successfully in the treatment of acute hyperammonaemia in patients with urea cycle disorders. They provide alternative pathways for waste nitrogen disposal and help maintain nitrogen homeostasis. However, we report three patients with hyperammonaemia who received inappropriate doses of intravenous sodium benzoate and sodium phenylacetate that resulted in severe complications. Ambiguous medical prescriptions and inadequate cross-checking of drug dosage by physicians, nurses and pharmacists were the main causes of these incidents. All the patients presented with alteration in mental status, Kussmaul respiration and a partially compensated metabolic acidosis with an increased anion gap. Two patients developed cerebral oedema and hypotension and died. The third survived after haemodialysis. Plasma levels of benzoate and phenylacetate were excessively high. The possible mechanisms of toxicity, management and safety measures are discussed.”

http://www.ncbi.nlm.nih.gov/pubmed/10801054

“Benzoate increased both the basal and post-glutamine ammonia levels. These results confirm what has already been observed in experimental animals and suggest a note of caution in the use of sodium benzoate in cirrhotic patients.”

American Journal Of Gastroenterology • December 2000

Effect of sodium benzoate on blood ammonia response to oral glutamine challenge in cirrhotic patients: a note of caution

Author information

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Abstract

OBJECTIVE

The administration of sodium benzoate provides an alternative pathway for the disposal of waste nitrogen and this substance has been used to treat patients with urea cycle defects and more recently cirrhotics with hepatic encephalopathy. The aim of the study was to assess the ammonia-lowering effect of benzoate in cirrhotic patients without overt hepatic encephalopathy.

METHODS

Glutamine challenge, a method to induce an increase of blood ammonia, was performed in six cirrhotics before and after 5 days of benzoate treatment (10 microg/day). Number Connection Test and Posner’s Attention Test were also performed before and after benzoate treatment.

RESULTS

Blood ammonia increased after the glutamine load both before (from 66 +/- 12 microg/dl to 123 +/- 34 microg/dl and 179 +/- 53 microg/dl after 30 and 60 min, respectively; ANOVA p = 0.0004) and after benzoate treatment (from 102 +/- 27 microg/dl to 185 +/- 49 microg/dl and 250 +/- 39 microg/dl after 30 and 60 min, respectively; ANOVA p = 0.00001). However, after benzoate treatment, the basal values (102 +/- 27 vs 66 +/- 12 microg/dl; p = 0.01) and peak increments of ammonia (166 +/- 56 microg/dl vs 102 +/- 40 microg/dl; p = 0.04) were significantly higher than before. The Number Connection test and the Posner’s test were not altered by benzoate treatment.

CONCLUSIONS

Benzoate increased both the basal and post-glutamine ammonia levels. These results confirm what has already been observed in experimental animals and suggest a note of caution in the use of sodium benzoate in cirrhotic patients.

http://www.ncbi.nlm.nih.gov/pubmed/11151894

Hepatology • July 1992

Sodium benzoate in the treatment of acute hepatic encephalopathy: a double-blind randomized trial

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Abstract

A prospective randomized double-blind study was conducted to evaluate the efficacy of sodium benzoate in the treatment of acute portal-systemic encephalopathy. Seventy-four consecutive patients with cirrhosis or surgical portasystemic anastomosis and hepatic encephalopathy of less than 7 days duration were randomized to receive lactulose (dose adjusted for 2 or 3 semiformed stools/day) or sodium benzoate (5 gm twice daily). Assessment of response included mental status, asterixis, arterial ammonia level, electroencephalogram and number-connection test. Each was given a score between 0 and 4+. A portal-systemic encephalopathy index was calculated with these scores. Visual, auditory and somatosensory evoked potentials and a battery of psychometric tests for intelligence and memory were also performed to assess improvement. Thirty-eight patients received sodium benzoate; 36 took lactulose. Thirty patients (80%) receiving sodium benzoate and 29 (81%) receiving lactulose recovered; the remaining patients died. Improvement in portal-systemic encephalopathy parameters occurred in both treatment groups and was similar (p greater than 0.1). Electroencephalogram and evoked potentials were not as helpful as mental status in assessing of recovery. Psychometric test scores remained abnormal after recovery of mental status (21 to 42 days) and were probably too sensitive for monitoring of these patients. The incidence of side effects was similar in the two treatment groups. The cost of lactulose for one course of therapy was 30 times that of sodium benzoate. We conclude that sodium benzoate is a safe and effective alternative to lactulose in the treatment of acute portasystemic encephalopathy.

http://www.ncbi.nlm.nih.gov/pubmed/1618465

“We suggested that sodium benzoate is a safe, efficacious and comfortable alternate treatment for portal systemic encepalopathy.”

Revista de Investigacion Clinica • July 1990

Sodium benzoate in portal-systemic-encephalopathy-induced blood ammonia normalization and clinical improvement. Interim report of a double-blind multicenter trial

Author information

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Abstract

To investigate the therapeutic efficacy of sodium benzoate (SB) in a cirrotic population with chronic portal systemic encepalopathy (PSE), we performed a double blind, randomised, multicentric, clinical trial, comparing SB versus a standard therapy of lactitol (LA). To perform the study blind, syrups containing the two drugs were prepared. To date 27 patients have been studied. Of these, 12 received SB (5.6 g/day) and 15 received LA (29 g/day). Standard PSE parameters were assessed and hippurate urinary excretion was measured before and after the trial. For the SB group, basal and final PSE index were 0.39 +/- 0.16 and 0.17 +/- 0.1 respectively ($p < 0.001$). The Group on LA had a PSE index of 0.40 + 0.1 and 0.23 +/- 0.18 (basal and final respectively) ($p < 0.001$). The final hippurate excretion for SB group was 2498.9 mg/24 h. The hippurate excretion for the LA group suffer no changes (traces). No serious side effects were observed with either therapy. We suggested that SB is a safe, efficacious and comfortable alternate treatment for PSE.

http://www.ncbi.nlm.nih.gov/pubmed/19256155

Revista de Investigacion Clinica • July 1990

Rationale for the use of sodium benzoate in clinical hepatology

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Abstract

Sodium benzoate is widely used in the Alimentary Industry at low doses for its antimicrobial action. It has also been used as a liver function test. The principle is to evaluate the liver capacity for conjugation of glycine to benzoic acid and to form hippuric acid which is excreted in the urine. In hyperammonemic syndromes, secondary to enzymatic deficiency of the urea cicle, sodium benzoate has the property to act as an alternative way of nitrogen excretion to urinary hippurate instead of urea. Recently, it has been proposed as a therapeutic alternative in cirrhotic patients with portal systemic encephalopathy. Historical, biochemical and clinical data which constitute the principles to validate its clinical application in Hepatology are reviewed in this manuscript.

http://www.ncbi.nlm.nih.gov/pubmed/19256146

The Journal Of General Physiology • May 1922

Effect of cocaine on the growth of lupinus albus. A contribution to the comparative pharmacology of animal and plant protoplasm

Author information

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Abstract

“1. The effects of cocaine and its decomposition products were studied on the growth of the young roots of Lupinus albus. 2. The results obtained were compared with similar experiments on animal tissues. 3. It was found that, while cocaine is the most toxic of these compounds studied for animal tissues, it was of comparatively low toxicity in respect to its effect on the growth of roots. On the other hand, sodium benzoate, being practically non-toxic for animals, was the most toxic of the compounds studied for the plant roots.”

Full text with 9 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2140515/pdf/573.pdf

CHAPTER TWENTY-FIVE

Coffee & Cocoa

The Peer Review

The genus Coffea is native to tropical Africa, Madagascar, and the Comoros, Mauritius and Réunion in the Indian Ocean. The plant was exported from Africa to countries around the world and coffee plants are now cultivated in over 70 countries, primarily in the equatorial regions of the Americas, Southeast Asia, India, and Africa. The two most commonly grown are the highly regarded arabica, and the less sophisticated but stronger and more hardy robusta.

Coffee is slightly acidic and can have a stimulating effect on humans because of its caffeine content. Clinical studies indicate that moderate coffee consumption is benign or mildly beneficial in healthy adults, with continuing research on whether long-term consumption inhibits cognitive decline during aging or lowers the risk of some forms of cancer.

The earliest credible evidence of coffee-drinking appears in the middle of the 15th century in the Sufi shrines of Yemen. It was here in Arabia that coffee seeds were first roasted and brewed in a similar way to how it is now prepared. Coffee seeds were first exported from Eastern Africa to Yemen, as the coffee plant is thought to have been indigenous to the former. Yemeni traders took coffee back to their homeland and began to cultivate the seed. By the 16th century, it had reached the rest of the Middle East, Persia, Turkey, and northern Africa. From there, it spread to Europe and the rest of the world.

Coffee is a major export commodity: it is the top agricultural export for numerous countries and is among the world's largest legal agricultural exports. It is one of the most valuable commodities exported by developing countries. Green (unroasted) coffee is one of the most traded agricultural commodities in the world. Some controversy is associated with coffee cultivation and the way developed countries trade with developing nations and the impact of its cultivation on the environment, in regards to clearing of land for coffee-growing and water use. Consequently, fair trade coffee and organic coffee are an expanding market.

Chocolate is a typically sweet, usually brown, food preparation of Theobroma cacao seeds, roasted and ground, often flavored, as with vanilla. It is made in the form of a liquid, paste, or in a block, or used as a flavoring ingredient in other foods. Cacao has been cultivated by many cultures for at least three millennia in Mesoamerica. The earliest evidence of use traces to the Mokaya (Mexico and Guatemala), with evidence of chocolate beverages dating back to 1900 BC. In fact, the majority of Mesoamerican people made chocolate beverages, including the Maya and Aztecs, who made it into a beverage known as xocolātl, a Nahuatl word meaning "bitter water". The seeds of the cacao tree have an intense bitter taste and must be fermented to develop the flavor. After fermentation, the beans are dried, cleaned, and roasted. The shell is removed to produce cacao nibs, which are then ground to cocoa mass, pure chocolate in rough form. Because the cocoa mass is usually liquefied before being molded with or without other ingredients, it is called chocolate liquor. The liquor also may be processed into two components: cocoa solids and cocoa butter. Unsweetened baking chocolate contains primarily cocoa solids and cocoa butter in varying proportions. Much of the chocolate consumed today is in the form of sweet chocolate, a combination of cocoa solids, cocoa butter or other fat, and sugar. Milk chocolate is sweet chocolate that additionally contains milk powder or condensed milk.

Cocoa solids are a source of flavonoids and alkaloids, such as theobromine, phenethylamine and caffeine. Western Africa produces almost two-thirds of the world's cocoa, with Ivory Coast growing almost half of it. In 2009, Salvation Army International Development stated that child labor and the human trafficking and slavery of child laborers are used in African cocoa cultivation.

Human Psychopharmacology • January 2016

Acute personalized habitual caffeine doses improve attention and have selective effects when considering the fractionation of executive functions

Author information

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Abstract

Caffeine is widely used, often consumed with food, and improves simple and complex/executive attention under fasting conditions. We investigated whether these cognitive effects are observed when personalized habitual doses of caffeine are ingested by caffeine consumers, whether they are influenced by nutriments and if various executive domains are susceptible to improvement. This was a double-blind, placebo-controlled study including 60 young, healthy, rested males randomly assigned to one of four treatments: placebo fasting, caffeine fasting, placebo meal and caffeine meal. Caffeine doses were individualized for each participant based on their self-reported caffeine consumption at the time of testing (morning). The test battery included measures of simple and sustained attention, executive domains (inhibiting, updating, shifting, dual tasking, planning and accessing long-term memory), control measures of subjective alterations, glucose and insulin levels, skin conductance, heart rate and pupil dilation. Regardless of meal intake, acute habitual doses of caffeine decreased fatigue, and improved simple and sustained attention and executive updating. This executive effect was not secondary to the habitual weekly dose consumed, changes in simple and sustained attention, mood, meal ingestion and increases in cognitive effort. We conclude that the morning caffeine “fix” has positive attentional effects and selectively improved executive updating whether or not caffeine is consumed with food.

http://www.ncbi.nlm.nih.gov/pubmed/26621326

Dementia, Geriatrics And Cognitive Disorders • March 2016

The Effect of Prior Caffeine Consumption on Neuropsychological Test Performance: A Placebo-Controlled Study

Author information

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Abstract

BACKGROUND

The aim of this study was to investigate whether the prior consumption of 200 mg of pure caffeine affected neuropsychological test scores in a group of elderly participants aged over 60 years.

METHOD

Using a double-blind placebo versus caffeine design, participants were randomly assigned to receive 200 mg of caffeine or placebo. A neuropsychological assessment testing the domains of general cognitive function, processing speed, semantic memory, episodic memory, executive function, working memory and short-term memory was carried out.

RESULTS

Significant interaction effects between age, caffeine and scores of executive function and processing speed were found; participants who had received caffeine showed a decline in performance with increasing age. This effect was not seen for participants who received placebo.

CONCLUSION

The results highlight the need to consider and control prior caffeine consumption when scoring neuropsychological assessments in the elderly, which is important for accuracy of diagnosis and corresponding normative data.

http://www.ncbi.nlm.nih.gov/pubmed/27002645

“... executive functioning improvements as a result of a ‘typical’ dose of caffeine may only be detected by the use of more real-world, ecologically valid tasks.”

Appetite • May 2016

Investigating the effects of caffeine on executive functions using traditional Stroop and a new ecologically-valid virtual reality task, the Jansari assessment of Executive Functions (JEF©)

Author information

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Abstract

OBJECTIVE

Caffeine has been shown to have effects on certain areas of cognition, but in executive functioning the research is limited and also inconsistent. One reason could be the need for a more sensitive measure to detect the effects of caffeine on executive function. This study used a new non-immersive virtual reality assessment of executive functions known as JEF© (the Jansari Assessment of Executive Function) alongside the ‘classic’ Stroop Colour-Word task to assess the effects of a normal dose of caffeinated coffee on executive function.

METHOD

Using a double-blind, counterbalanced within participants procedure 43 participants were administered either a caffeinated or decaffeinated coffee and completed the ‘JEF©’ and Stroop tasks, as well as a subjective mood scale and blood pressure pre- and post condition on two separate occasions a week apart. JEF© yields measures for eight separate aspects of executive functions, in addition to a total average score.

RESULTS

Findings indicate that performance was significantly improved on the planning, creative thinking, event-, time- and action-based prospective memory, as well as total JEF© score following caffeinated coffee relative to the decaffeinated coffee. The caffeinated beverage significantly decreased reaction times on the Stroop task, but there was no effect on Stroop interference.

CONCLUSION

The results provide further support for the effects of a caffeinated beverage on cognitive functioning. In particular, it has demonstrated the ability of JEF© to detect the effects of caffeine across a number of executive functioning constructs, which weren’t shown in the Stroop task, suggesting executive functioning improvements as a result of a ‘typical’ dose of caffeine may only be detected by the use of more real-world, ecologically valid tasks.

http://www.ncbi.nlm.nih.gov/pubmed/27215836

Journal Of Environmental Biology • March 2015

Impacts of biotic and abiotic stress on major quality attributing metabolites of coffee beans

Vaddadi S, Parvatam G.

Abstract

Biotic stress factors such as Rhizopus oligosporus and Aspergillus niger mycelial extracts and abiotic elements methyljasmonate (MJ) and salicylic acid (SA), when administered through floral spray to Coffea canephora, showed significant influence on major bioactive metabolites of beans. Up to 42% caffeine, 39% theobromine and 46% trigonelline, along with 32% cafestol and kahweol content elevation was evident under respective elicitor treatments. Over all, the surge in respective metabolites depends on elicitor stress type and concentration. Abiotic factors MJ and SA were found to be efficient at 1 to 5 microM concentration in augmenting all the metabolites, compared to R. oligosporus and A. niger spray at 0.5-2.0% wherein the response was moderate as compared to abiotic stress, however significant compared to control. Though this elevation in caffeine, theobromine, cafestol and kahweol is not warranted from quality point of view, increase in trigonelline improves coffee quality. Besides increase in metabolites, stress mediated augmentation of bioactive compounds in coffee has a wide scope for studying gene expression pattern.

http://www.ncbi.nlm.nih.gov/pubmed/25895259

Journal Of Nutrition, Health And Aging • March 2015

Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review

Author information

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Abstract

A prolonged preclinical phase of more than two decades before the onset of dementia suggested that initial brain changes of Alzheimer's disease (AD) and the symptoms of advanced AD may represent a unique continuum. Given the very limited therapeutic value of drugs currently used in the treatment of AD and dementia, preventing or postponing the onset of AD and delaying or slowing its progression are becoming mandatory. Among possible reversible risk factors of dementia and AD, vascular, metabolic, and lifestyle-related factors were associated with the development of dementia and late-life cognitive disorders, opening new avenues for the prevention of these diseases. Among diet-associated factors, coffee is regularly consumed by millions of people around the world and owing to its caffeine content, it is the best known psychoactive stimulant resulting in heightened alertness and arousal and improvement of cognitive performance. Besides its short-term effect, some case-control and cross-sectional and longitudinal population-based studies evaluated the long-term effects on brain function and provided some evidence that coffee, tea, and caffeine consumption or higher plasma caffeine levels may be protective against cognitive impairment/decline and dementia. In particular, several cross-sectional and longitudinal population-based studies suggested a protective effect of coffee, tea, and caffeine use against late-life cognitive impairment/decline, although the association was not found in all cognitive domains investigated and there was a lack of a distinct dose-response association, with a stronger effect among women than men. The findings on the association of coffee, tea, and caffeine consumption or plasma caffeine levels with incident mild cognitive impairment and its progression to dementia were too limited to draw any conclusion. Furthermore, for dementia and AD prevention, some studies with baseline examination in midlife pointed to a lack of association, although other case-control and longitudinal population-based studies with briefer follow-up periods supported favourable effects of coffee, tea, and caffeine consumption against AD. Larger studies with longer follow-up periods should be encouraged, addressing other potential bias and confounding sources, so hopefully opening new ways for diet-related prevention of dementia and AD.

http://www.ncbi.nlm.nih.gov/pubmed/25732217

Chinese Journal Of Traumatology • April 2015

Chronic caffeine exposure attenuates blast-induced memory deficit in mice

Author information

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Abstract

OBJECTIVE

To investigate the effects of three different ways of chronic caffeine administration on blast- induced memory dysfunction and to explore the underlying mechanisms.

METHODS

Adult male C57BL/6 mice were used and randomly divided into five groups: control: without blast exposure, con-water: administrated with water continuously before and after blast-induced traumatic brain injury (bTBI), con-caffeine: administrated with caffeine continuously for 1 month before and after bTBI, pre-caffeine: chronically administrated with caffeine for 1 month before bTBI and withdrawal after bTBI, post-caffeine: chronically administrated with caffeine after bTBI. After being subjected to moderate intensity of blast injury, mice were recorded for learning and memory performance using Morris water maze (MWM) paradigms at 1, 4, and 8 weeks post-blast injury. Neurological deficit scoring, glutamate concentration, proinflammatory cytokines production, and neuropathological changes at 24 h, 1, 4, and 8 weeks post-bTBI were examined to evaluate the brain injury in early and prolonged stages. Adenosine A1 receptor expression was detected using qPCR.

RESULTS

All of the three ways of chronic caffeine exposure ameliorated blast-induced memory deficit, which is correlated with the neuroprotective effects against excitotoxicity, inflammation, astrogliosis and neuronal loss at different stages of injury. Continuous caffeine treatment played positive roles in both early and prolonged stages of bTBI; pre-bTBI and post-bTBI treatment of caffeine tended to exert neuroprotective effects at early and prolonged stages of bTBI respectively. Up-regulation of adenosine A1 receptor expression might contribute to the favorable effects of chronic caffeine consumption.

CONCLUSION

Since caffeinated beverages are widely consumed in both civilian and military personnel and are convenient to get, the results may provide a promising prophylactic strategy for blast-induced neurotrauma and the consequent cognitive impairment.

http://www.ncbi.nlm.nih.gov/pubmed/26764541

“These results indicate that High-fat diet could exacerbate the dysfunction of lipid metabolism and the susceptibility to metabolic syndrome induced by Prenatal caffeine exposure, and the female offspring are more sensitive to High-fat diet-induced neuroendocrine metabolic dysfunction than their male counterparts.“

Toxicology And Applied Pharmacology • May 2015

Gender-specific increase in susceptibility to metabolic syndrome of offspring rats after prenatal caffeine exposure with post-weaning high-fat diet

Author information

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Abstract

Prenatal caffeine exposure (PCE) alters the hypothalamic-pituitary-adrenocortical (HPA) axis-associated neuroendocrine metabolic programming and induces an increased susceptibility to metabolic syndrome (MS) in intrauterine growth retardation (IUGR) offspring rats. High-fat diet (HFD) is one of the main environmental factors accounting for the incidence of MS. In this study, we aimed to clarify the gender-specific increase in susceptibility to MS in offspring rats after PCE with post-weaning HFD. Maternal Wistar rats were administered with caffeine (120mg/kg·d) from gestational day 11 until delivery. The offspring rats with normal diet or HFD were euthanized at postnatal week 24, and blood samples were collected. Results showed that PCE not only reduced serum adrenocorticotropic hormone (ACTH) and corticosterone levels, but also enhanced serum glucose, triglyceride and total cholesterol (TCH) concentrations in the offspring rats. Moreover, several interactions among PCE, HFD and gender were observed by a three-way ANOVA analysis. In PCE offspring, HFD could aggravate the degree of increased serum triglyceride level. Meanwhile, serum corticosterone levels of females were decreased more obviously than those of males in PCE offspring. The results also revealed interactions between HFD and gender in the levels of serum ACTH, triglyceride and TCH, which were changed more evidently in female HFD offspring. These results indicate that HFD could exacerbate the dysfunction of lipid metabolism and the susceptibility to MS induced by PCE, and the female offspring are more sensitive to HFD-induced neuroendocrine metabolic dysfunction than their male counterparts.

http://www.ncbi.nlm.nih.gov/pubmed/25771125

“In this large sample of men and women apparently free of clinically evident cardiovascular disease, moderate coffee consumption was associated with a lower prevalence of subclinical coronary atherosclerosis.”

Heart • May 2015

Coffee consumption and coronary artery calcium in young and middle-aged asymptomatic adults

Author information

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Abstract

OBJECTIVE

To investigate the association between regular coffee consumption and the prevalence of coronary artery calcium (CAC) in a large sample of young and middle-aged asymptomatic men and women.

METHODS

This cross-sectional study included 25 138 men and women (mean age 41.3 years) without clinically evident cardiovascular disease who underwent a health screening examination that included a validated food frequency questionnaire and a multidetector CT to determine CAC scores. We used robust Tobit regression analyses to estimate the CAC score ratios associated with different levels of coffee consumption compared with no coffee consumption and adjusted for potential confounders.

RESULTS

The prevalence of detectable CAC (CAC score >0) was 13.4% (n=3364), including 11.3% prevalence for CAC scores 1-100 (n=2832), and 2.1% prevalence for CAC scores >100 (n=532). The mean ±SD consumption of coffee was 1.8±1.5 cups/day. The multivariate-adjusted CAC score ratios (95% CIs) comparing coffee drinkers of <1, 1-<3, 3-<5, and ≥5 cups/day to non-coffee drinkers were 0.77 (0.49 to 1.19), 0.66 (0.43 to 1.02), 0.59 (0.38 to 0.93), and 0.81 (0.46 to 1.43), respectively (p for quadratic trend=0.02). The association was similar in subgroups defined by age, sex, smoking status, alcohol consumption, status of obesity, diabetes, hypertension, and hypercholesterolaemia.

CONCLUSIONS

In this large sample of men and women apparently free of clinically evident cardiovascular disease, moderate coffee consumption was associated with a lower prevalence of subclinical coronary atherosclerosis.

http://www.ncbi.nlm.nih.gov/pubmed/25732752

“The use of Artificial Sweeteners has increased and become more widespread, and consequently Artificial Sweeteners have appeared in aquatic environments around the world. However, their safety to the health of humans and wildlife remains inconclusive. We found that the ranking of developmental toxicity was SAC > CAF > ASP > SUC, **and there was a cumulative effect when Caffeine was combined with the sweeteners.**”

Springerplus • September 2015

Assessing developmental toxicity of caffeine and sweeteners in medaka (Oryzias latipes)

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Abstract

The use of artificial sweeteners (ASWs) has increased and become more widespread, and consequently ASWs have appeared in aquatic environments around the world. However, their safety to the health of humans and wildlife remains inconclusive. In this study, using medaka embryos (Oryzias latipes), we investigated developmental toxicity of aspartame (ASP) and saccharin (SAC). Since ASWs are often consumed with caffeine (CAF) and CAF with sucrose (SUC), we tested biological activities of these four substances and the mixtures of CAF with each sweetener. The embryos were exposed to ASP at 0.2 and 1.0 mM, SAC at 0.005 and 0.050 mM, CAF at 0.05 and 0.5 mM, or SUC at 29 and 146 mM, starting from less than 5 h post fertilization until hatch. Control embryos were treated with embryo solution only. Several endpoints were used to evaluate embryonic development. Some of the hatchlings were also tested for anxiety-like behavior with the white preference test. The results showed that all four substances and the mixtures of CAF with the sweeteners affected development. The most sensitive endpoints were the heart rate, eye density, and hatchling body length. The hatchlings of several treatment groups also exhibited anxiety-like behavior. We then used the Integrated Biological Response (IBR) as an index to evaluate the overall developmental toxicity of the substances. We found that the ranking of developmental toxicity was SAC > CAF > ASP > SUC, and there was a cumulative effect when CAF was combined with the sweeteners.

Full text, graphs and charts with 42 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4562911/

“Consumption of cocoa flavanol improves regional cerebral perfusion in older adults. This provides evidence for a possible acute mechanism by which cocoa flavanols are associated with benefits for cognitive performance.”

Psychopharmacology (Berlin) • September 2015

The effect of flavanol-rich cocoa on cerebral perfusion in healthy older adults during conscious resting state: a placebo controlled, crossover, acute trial

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Abstract

RATIONALE

There has recently been increasing interest in the potential of flavanols, plant-derived compounds found in foods such as fruit and vegetables, to ameliorate age-related cognitive decline. Research suggests that cocoa flavanols improve memory and learning, possibly as a result of their anti-inflammatory and neuroprotective effects. These effects may be mediated by increased cerebral blood flow (CBF), thus, stimulating neuronal function.

OBJECTIVES

The present study employed arterial spin labelling functional magnetic resonance imaging to explore the effect of a single acute dose of cocoa flavanols on regional CBF.

METHODS

CBF was measured pre- and post-consumption of low (23 mg) or high (494 mg) 330 ml equicaloric flavanol drinks matched for caffeine, theobromine, taste and appearance according to a randomized counterbalanced crossover double-blind design in eight males and ten females, aged 50-65 years. Changes in perfusion from pre- to post-consumption were calculated as a function of each drink.

RESULTS

Significant increases in regional perfusion across the brain were observed following consumption of the high flavanol drink relative to the low flavanol drink, particularly in the anterior cingulate cortex and the central opercular cortex of the parietal lobe.

CONCLUSIONS

Consumption of cocoa flavanol improves regional cerebral perfusion in older adults. This provides evidence for a possible acute mechanism by which cocoa flavanols are associated with benefits for cognitive performance.

Full text with 45 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4534492/

Bratisl Lek Listy • October 2015

The perspective of caffeine and caffeine derived compounds in therapy

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Abstract

Caffeine (1,3,7-trimethylxanthine) is a plant secondary metabolite with a significant impact on multiple processes and regulatory pathways in the body. Though major part of the population meets caffeine via coffee, tea or chocolate, it has also an important role in pharmacology and it is used as a supplementary substance in medicaments. Currently, the ability of caffeine to ameliorate some neurodegenerative disorders is proved in some studies. This review describes basic data about caffeine including toxicity, pharmacokinetics, biological mechanism of the action, and metabolism. Beside this, promising applications of caffeine, new medicaments and derivatives are discussed. Relevant papers and inventions are depicted in the manuscript. Caffeine is a pharmacologically promising substance that deserves big consideration in the current research and development. The compound has several reasons to be an object of scientific interest and to be used for pharmacology purposes. Despite an extensive research for a long time, no significantly negative effects on human health were proved hence caffeine can be considered as a completely safe compound. The recent data about amelioration of neurodegenerative and other disorders are promising and deserving more work on the issue. ARTICLE HIGHLIGHTS: Caffeine is a purine alkaloid from plants and it has a broad use in current pharmacology. Caffeine is a competitive antagonist of neurotransmitter adenosine on adenosine receptors. The substance is added as a supplementary to drugs and food.Besides interfering on adenosine receptors, caffeine interacts with acetylcholinesterase, monoamine oxidase, phosphodiesterase, ryanodine receptors and others.Current research is devoted to the role of caffeine in neurodegenerative diseases and immunity alteration. New chemical compounds based on caffeine moiety are prepared (Tab. 4, Fig. 6, Ref. 149).Bratisl Lek Listy. 2015;116(9):520-30.

http://www.ncbi.nlm.nih.gov/pubmed/26435014

Journal Of Alzheimers Disease • November 2015

Does Caffeine Consumption Modify Cerebrospinal Fluid Amyloid-ß Levels in Patients with Alzheimer's Disease?

Author information

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Abstract

Caffeine may be protective against Alzheimer's disease (AD) by modulating amyloid-ß (Aß) metabolic pathways. The present work aimed to study a possible association of caffeine consumption with the cerebrospinal fluid (CSF) biomarkers, particularly Aß. The study included 88 patients with AD or mild cognitive impairment. The consumption of caffeine and theobromine was evaluated using a validated food questionnaire. Quantification of caffeine and main active metabolites was performed with liquid chromatography coupled to tandem mass spectrometry. The levels of A(1-42), total tau, and phosphorylated tau in the CSF were determined using sandwich ELISA methods and other Aß species, Aß(X-38), Aß(X-40), and Aß(X-42), with the MSD Aß Triplex assay. The concentration of caffeine was 0.79±1.15 µg/mL in the CSF and 1.20±1.88 µg/mL in the plasma. No correlation was found between caffeine consumption and Aß42 in the CSF. However, a significant positive correlation was found between the concentrations of theobromine, both in the CSF and in the plasma, with Aß42 in the CSF. Theobromine in the CSF was positively correlated with the levels of other xanthines in the CSF, but not in the plasma, suggesting that it may be formed by central metabolic pathways. In conclusion, caffeine consumption does not modify the levels of CSF biomarkers, and does not require to be controlled for when measuring CSF biomarkers in a clinical setting. Since theobromine is associated with a favorable Aß profile in the CSF, the possibility that it might have a protective role in AD should be further investigated.

http://www.ncbi.nlm.nih.gov/pubmed/26401784

“In conclusion, prenatal caffeine exposure induced a poor quality of articular cartilage in male adult offspring fed a high-fat die. This finding was shown to be due to cholesterol accumulation in the cartilage, which may have resulted from intrauterine reduced activity of the insulin-like growth factor1 signaling pathway.”

Science Reports • December 2015

Prenatal caffeine exposure induces a poor quality of articular cartilage in male adult offspring rats via cholesterol accumulation in cartilage

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Abstract

Epidemiological investigations indicate that osteoarthritis is associated with intrauterine growth retardation (IUGR) and abnormal cholesterol metabolism. Our previous studies showed that prenatal caffeine exposure (PCE) induced chondrogenesis retardation in IUGR offspring rats. The current study sought to investigate the effects of PCE on male IUGR offspring rats' articular cartilage, and the mechanisms associated with abnormal cholesterol metabolism. Based on the results from both male fetal and adult fed a high-fat diet (HFD) studies of rats that experienced PCE (120 mg/kg.d), the results showed a poor quality of articular cartilage and cholesterol accumulation in the adult PCE group. Meanwhile, the serum total cholesterol and low-density lipoprotein-cholesterol concentrations were increased in adult PCE offspring. We also observed lower expression of insulin-like growth factor1 (IGF1) and impaired cholesterol efflux in adult articular cartilage. Furthermore, the expression of cartilage functional genes, components of the IGF1 signaling pathway and cholesterol efflux pathway related genes were decreased in PCE fetal cartilage. In conclusion, PCE induced a poor quality of articular cartilage in male adult offspring fed a HFD. This finding was shown to be due to cholesterol accumulation in the cartilage, which may have resulted from intrauterine reduced activity of the IGF1 signaling pathway.

Full text, graphs, charts, images and 59 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4671025/

“Cocoa products present great health potential due to their high content of polyphenols, mainly of flavanols. However, the antioxidant, anti-inflammatory and other health effects of regularly consuming cocoa products seem to depend on the intake and health status of the consumer, etc. and need to be further clarified.”

British Journal Of Nutrition • January 2014

Regular consumption of a cocoa product improves the cardiometabolic profile in healthy and moderately hypercholesterolaemic adults

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Abstract

Cocoa products present great health potential due to their high content of polyphenols, mainly of flavanols. However, the antioxidant, anti-inflammatory and other health effects of regularly consuming cocoa products seem to depend on the intake and health status of the consumer, etc. and need to be further clarified. A randomised, controlled, cross-over, free-living study was carried out in healthy (n 24) and moderately hypercholesterolaemic (>2000 mg/l, n 20) subjects to assess the influence of regularly consuming (4 weeks) two servings (15 g each) of a cocoa product rich in fibre (containing 33·9 % of total dietary fibre (TDF) and 13·9 mg/g of soluble polyphenols) in milk v. consuming only milk (control) on (1) serum lipid and lipoprotein profile, (2) serum malondialdehyde levels, carbonyl groups, ferric reducing/antioxidant power, oxygen radical absorbance capacity and free radical-scavenging capacity, (3) IL-1ß, IL-6, TNF-ß, IL-10, IL-8, monocyte chemoattractant protein-1, and vascular and intracellular cell adhesion molecule levels, and (4) systolic and diastolic blood pressure and heart rate. Throughout the study, the diet and physical activity of the volunteers, as well as any possible changes in weight or other anthropometric parameters, were also evaluated. The intake of TDF increased ($P< 0·001$) to the recommended levels. Serum HDL-cholesterol (HDL-C) levels were increased ($P< 0·001$), whereas glucose ($P= 0·029$), IL-1ß ($P= 0·001$) and IL-10 ($P= 0·001$) levels were decreased. The rest of the studied cardiovascular parameters, as well as the anthropometric ones, remained similar. In conclusion, regularly consuming a cocoa product with milk improves cardiovascular health by increasing HDL-C levels and inducing hypoglycaemic and anti-inflammatory effects in healthy and hypercholesterolaemic individuals without causing weight gain.

http://www.ncbi.nlm.nih.gov/pubmed/23823716

Life Sciences • April 2014

Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases: a review

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Abstract

Caffeine is the most consumed pychostimulant in the world, and it is known to affect basic and fundamental human processes such as sleep, arousal, cognition and learning and memory. It works as a nonselective blocker of adenosine receptors (A1, A2a, A2b and A3) and has been related to the regulation of heart rate, the contraction/relaxation of cardiac and smooth muscles, and the neural signaling in the central nervous system (CNS). Since the late 1990s, studies using adenosine receptor antagonists, such as Caffeine, to block the A1 and A2a adenosine receptor subtypes have shown to reduce the physical, cellular and molecular damages caused by a spinal cord injury (SCI) or a stroke (cerebral infarction) and by other neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. Interestingly, other studies using adenosine receptor agonists have also shown to provide a neuroprotective effect on various models of neurodegenerative diseases through the reduction of excitatory neurotransmitter release, apoptosis and inflammatory responses, among others. The seemingly paradoxical use of both adenosine receptor agonists and antagonists as neuroprotective agents has been attributed to differences in dosage levels, drug delivery method, extracellular concentration of excitatory neurotransmitters and stage of disease progression. We discuss and compare recent findings using both antagonists and agonists of adenosine receptors in animal models and patients that have suffered spinal cord injuries, brain strokes, and Parkinson's and Alzheimer's diseases. Additionally, we propose alternative interpretations on the seemingly paradoxical use of these drugs as potential pharmacological tools to treat these various types of neurodegenerative diseases.

Full text, graphs, charts and 106 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4115368/

Psychopharmacology (Berlin) • January 2013

Caffeine as an attention enhancer: reviewing existing assumptions

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Abstract

RATIONALE

Despite the large number of studies on the behavioural effects of caffeine, an unequivocal conclusion had not been reached. In this review, we seek to disentangle a number of questions.

OBJECTIVE

Whereas there is a general consensus that caffeine can improve performance on simple tasks, it is not clear whether complex tasks are also affected, or if caffeine affects performance of the three attention networks (alerting, orienting and executive control). Other questions being raised in this review are whether effects are more pronounced for higher levels of caffeine, are influenced by habitual caffeine use and whether there effects are due to withdrawal reversal.

METHOD

Literature review of double-blind placebo controlled studies that assessed acute effects of caffeine on attention tasks in healthy adult volunteers.

RESULTS

Caffeine improves performance on simple and complex attention tasks, and affects the alerting, and executive control networks. Furthermore, there is inconclusive evidence on dose-related performance effects of caffeine, or the influence of habitual caffeine consumption on the performance effects of caffeine. Finally, caffeine's effects cannot be attributed to withdrawal reversal.

CONCLUSIONS

Evidence shows that caffeine has clear beneficial effects on attention, and that the effects are even more widespread than previously assumed.

http://www.ncbi.nlm.nih.gov/pubmed/23241646

“In this study we show that in rats paraxanthine has a stronger locomotor activating effect than caffeine or the two other main metabolites of caffeine, theophylline and theobromine.”

Neuropharmacology • April 2013

Psychostimulant pharmacological profile of paraxanthine, the main metabolite of caffeine in humans

Author information

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Abstract

Caffeine induces locomotor activation by its ability to block adenosine receptors. Caffeine is metabolized to several methylxanthines, with paraxanthine being the main metabolite in humans. In this study we show that in rats paraxanthine has a stronger locomotor activating effect than caffeine or the two other main metabolites of caffeine, theophylline and theobromine. As previously described for caffeine, the locomotor activating doses of paraxanthine more efficiently counteract the locomotor depressant effects of an adenosine A(1) than an adenosine A(2A) receptor agonist. In drug discrimination experiments in rats trained to discriminate a maximal locomotor activating dose of caffeine, paraxanthine, unlike theophylline, generalized poorly to caffeine suggesting the existence of additional mechanisms other than adenosine antagonism in the behavioral effects of paraxanthine. Pretreatment with the nitric oxide inhibitor N(G)-nitro-l-arginine methyl ester (l-NAME) reduced the locomotor activating effects of paraxanthine, but not caffeine. On the other hand, pretreatment with the selective cGMP-preferring phosphodiesterase PDE9 inhibitor BAY 73-6691, increased locomotor activity induced by caffeine, but not paraxanthine. Ex vivo experiments demonstrated that paraxanthine, but not caffeine, can induce cGMP accumulation in the rat striatum. Finally, in vivo microdialysis experiments showed that paraxanthine, but not caffeine, significantly increases extracellular levels of dopamine in the dorsolateral striatum, which was blocked by l-NAME. These findings indicate that inhibition of cGMP-preferring PDE is involved in the locomotor activating effects of the acute administration of paraxanthine. The present results demonstrate a unique psychostimulant profile of paraxanthine, which might contribute to the reinforcing effects of caffeine in humans.

Full text and 57 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3562388/

“Cocoa and flavonoids from cocoa might positively modulate these mechanisms with a putative role in cardiovascular protection.”

Current Opinions In Clinical Nutrition And Metabolic Care • November 2013

Protective effects of dark chocolate on endothelial function and diabetes

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Abstract

PURPOSE OF REVIEW

Relationship between cocoa consumption and cardiovascular disease, particularly focusing on clinical implications resulting from the beneficial effects of cocoa consumption on endothelial function and insulin resistance. This could be of clinical relevance and may suggest the mechanistic explanation for the reduced risk of cardiovascular events reported in the different studies after cocoa intake.

RECENT FINDINGS

Increasing evidence supports a protective effect of cocoa consumption against cardiovascular disease. Cocoa and flavonoids from cocoa have been described to improve endothelial function and insulin resistance. A proposed mechanism could be considered in the improvement of the endothelium-derived vasodilator nitric oxide by enhancing nitric oxide synthesis or by decreasing nitric oxide breakdown.

SUMMARY

The endothelium plays a pivotal role in the arterial homeostasis, and insulin resistance is the most important pathophysiological feature in various prediabetic and diabetic states. Reduced nitric oxide bioavailability with endothelial dysfunction is considered the earliest step in the pathogenesis of atherosclerosis. Further, insulin resistance could account, at least in part, for the endothelial dysfunction. Endothelial dysfunction has been considered an important and independent predictor of future development of cardiovascular risk and events. Cocoa and flavonoids from cocoa might positively modulate these mechanisms with a putative role in cardiovascular protection.

http://www.ncbi.nlm.nih.gov/pubmed/24100673

“... intervention studies strongly suggest that cocoa has several beneficial effects on cardiovascular health, including the lowering of blood pressure, the improvement of vascular function and glucose metabolism, and the reduction of platelet aggregation and adhesion.”

Current Hypertension Reports • August 2012

Cocoa, blood pressure, and vascular function

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Abstract

The consumption of a high amount of fruits and vegetables was found to be associated with a lower risk of coronary heart disease and stroke. Epidemiologically, a similar relationship has been found with cocoa, a naturally polyphenol-rich food. Obviously, double blind randomized studies are difficult to perform with cocoa and chocolate, respectively. However, intervention studies strongly suggest that cocoa has several beneficial effects on cardiovascular health, including the lowering of blood pressure, the improvement of vascular function and glucose metabolism, and the reduction of platelet aggregation and adhesion. Several potential mechanisms through which cocoa might exert its positive effects have been proposed, among them activation of nitric oxide synthase, increased bioavailability of nitric oxide as well as antioxidant, and anti-inflammatory properties. It is the aim of this review to summarize the findings of cocoa and chocolate on blood pressure and vascular function.

http://www.ncbi.nlm.nih.gov/pubmed/22684995

Rocz Panstw Zakl Hig • December 2012

Caffeine—common ingredient in a diet and its influence on human health

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Abstract

Caffeine is widely consumed by people of all ages. In the last period a market of caffeine-containing products, particularly energy drinks and food supplements increased. Caffeine for years is under discussion, whether has positive whether adverse impact on health. Children are a group of special anxieties. Caffeine is a stimulant of central nervous system and therefore is probably the most commonly used psychoactive substance in the world. The physiological effect of caffeine and the lack of nutrition value causes a great interest its impact on health, especially with reference to the risk of cardiovascular diseases. Results of scientific research are not clear. The influence of caffeine on the human body is conditioned with the individual metabolism of caffeine which also depends on many endogenic and environmental factors. According to the current knowledge moderate caffeine intake by healthy adults at a dose level of 400 mg a day is not associated with adverse effects, but it also depends on other health determinants of a lifestyle. Excessive caffeine consumption can cause negative health consequences such as psychomotor agitation, insomnia, headache, gastrointestinal complaints. Adverse effect of caffeine intoxication is classified in World Health Organization's International Classification of Diseases (ICD-10). Metabolism of caffeine by pregnant woman is slowed down. Caffeine and its metabolites pass freely across the placenta into a fetus. For this reason pregnant women should limit caffeine intake. Children and adolescents should also limit daily caffeine consumption. It results from the influence of caffeine on the central nervous system in the period of rapid growth and the final stage of brain development, calcium balance and sleep duration. Average daily caffeine consumption in European countries ranging from 280-490 mg. The highest caffeine intake is in Scandinavian countries what results from the great consumption of the coffee. As far as caffeine consumption by Polish population is concerned there is very few data in this subject so far. In the nineties of the previous century it was 141 mg per day, whereas according to recent survey daily caffeine intake by women from the Warsaw region was 251 mg and 15% of examined women consumed an excessive quantity of caffeine (> or = 400 mg). Smokers consume more caffeine than nonsmokers, similarly to persons with mental illnesses. With reference to the caffeine consumption it should be underline that caffeine content in coffee and tea beverages varies greatly depending on the method of brewing whereas the content of caffeine in many brands of energy drinks can much vary. This should be taken into account in the daily caffeine intake.

Full text in Polish with 50 references

http://www.ncbi.nlm.nih.gov/pubmed/22928360

Journal Of Alzheimers Disease • July 2011

Coffee intake in midlife and risk of dementia and its neuropathologic correlates

Author information

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Erratum in J Alzheimers Dis. 2013 Jan 1;36(4):809

Abstract

While animal data suggest a protective effect of caffeine on cognition, studies in humans remain inconsistent. We examined associations of coffee and caffeine intake in midlife with risk of dementia, its neuropathologic correlates, and cognitive impairment among 3494 men in the Honolulu-Asia Aging Study (mean age 52 at cohort entry, 1965-1968) examined for dementia in 1991-1993, including 418 decedents (1992-2004) who underwent brain autopsy. Caffeine intake was determined according to self-reported coffee, tea, and cola consumption at baseline. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for overall dementia, Alzheimer's disease (AD), vascular dementia (VaD), cognitive impairment (Cognitive Abilities Screening Instrument score <74), and neuropathologic lesions at death (Alzheimer lesions, microvascular ischemic lesions, cortical Lewy bodies, hippocampal sclerosis, generalized atrophy), according to coffee and caffeine intake. Dementia was diagnosed in 226 men (including 118 AD, 80 VaD), and cognitive impairment in 347. There were no significant associations between coffee or caffeine intake and risk of cognitive impairment, overall dementia, AD, VaD, or moderate/high levels of the individual neuropathologic lesion types. However, men in the highest quartile of caffeine intake (>/=411.0 mg/d) [corrected] were less likely than men in the lowest quartile (</=137.0 mg) [corrected] to have any of the lesion types (adjusted-OR, 0.45; 95% CI, 0.23-0.89; p, trend = 0.04). Coffee and caffeine intake in midlife were not associated with cognitive impairment, dementia, or individual neuropathologic lesions, although higher caffeine intake was associated with a lower odds of having any of the lesion types at autopsy.

Full text, graphs, charts and 29 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3731132/

Brain Cognition • December 2010

Acute caffeine consumption enhances the executive control of visual attention in habitual consumers

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Abstract

Recent work suggests that a dose of 200-400 mg caffeine can enhance both vigilance and the executive control of visual attention in individuals with low caffeine consumption profiles. The present study seeks to determine whether individuals with relatively high caffeine consumption profiles would show similar advantages. To this end, we examined the effects of four caffeine doses (0 mg, 100 mg, 200 mg, 400 mg) on low- and high-level visual attention in individuals with high consumption profiles (n=36), in a double-blind study using a repeated measures design. Results from the Attention Network Test indicated that caffeine enhanced both vigilance and the executive control of visual attention, but only at the highest administered dose (400 mg). We demonstrate that in habitual consumers high doses of caffeine can produce beneficial changes in visual attention. These results carry implications for the theorized interactions between caffeine, adenosine and dopamine in brain regions mediating visual attention.

http://www.ncbi.nlm.nih.gov/pubmed/20832925

Niger Journal Of Physiology And Science • June 2009

The comparative effects of chronic consumption of kola nut (Cola nitida) and caffeine diets on locomotor behaviour and body weights in mice

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Abstract

The comparative effects of chronic [28 days] consumption of kola nut and its active constituent, caffeine diets on locomotor behaviour and body weights in mice were investigated. Thirty adult Swiss white mice [15-30 g body weight], were used for the study. The open field-maze was employed for the evaluation of locomotor behaviour. Mice in the control group [n=10] were fed normal rodent chow, mice in the kola nut-fed group [n=10] were fed kola diet [25 % wt/wt of rodent chow] while those in the caffeine-fed group [n=10] were fed caffeine diet [0.66% wt/wt of rodent chow] for 4 weeks. All animals were allowed free access to clean drinking water. Daily food intake, water intake and body weight change were also measured. Daily food intake in the kola nut and caffeine-fed group of mice was significantly [$P<0.001$ respectively] lower than the control. There was also a significant [$P<0.001$] decrease in daily water intake in the caffeine-fed group compared to the control whereas, the apparent decrease of water intake in the kola nut-fed group was not significantly different from the control. Body weight change was also significantly [$P<0.001$ and $P<0.05$ respectively] lower in the kola nut and caffeine-fed groups of mice when compared to the control. The frequency of rearing in the open field was significantly [$P<0.01$] lower in the caffeine-fed group of mice when compared to the control. The frequency of grooming was also significantly [$P<0.05$] lower in the caffeine-fed group of mice when compared to the control. There was also a significant [$P<0.05$] decrease in the frequency of light-dark transitions in the light/dark transition box for the caffeine-fed group when compared to the control. The results showed that chronic consumption of kola nut and caffeine diets caused decrease in food intake and body weight. Consumption of caffeine-diet also significantly decreased water intake and locomotor activity. The effect of kola nut-diets on water intake and locomotor activity was not significant. Hence, the effect of kola nut on locomotor behaviour and water intake may not be due to caffeine only.

http://www.ncbi.nlm.nih.gov/pubmed/19826468

Sleep Medical Reviews • April 2008

Caffeine: sleep and daytime sleepiness

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Abstract

Caffeine is one of the most widely consumed psychoactive substances and it has profound effects on sleep and wake function. Laboratory studies have documented its sleep-disruptive effects. It clearly enhances alertness and performance in studies with explicit sleep deprivation, restriction, or circadian sleep schedule reversals. But, under conditions of habitual sleep the evidence indicates that caffeine, rather then enhancing performance, is merely restoring performance degraded by sleepiness. The sleepiness and degraded function may be due to basal sleep insufficiency, circadian sleep schedule reversals, rebound sleepiness, and/or a withdrawal syndrome after the acute, over-night, caffeine discontinuation typical of most studies. Studies have shown that caffeine dependence develops at relatively low daily doses and after short periods of regular daily use. Large sample and population-based studies indicate that regular daily dietary caffeine intake is associated with disturbed sleep and associated daytime sleepiness. Further, children and adolescents, while reporting lower daily, weight-corrected caffeine intake, similarly experience sleep disturbance and daytime sleepiness associated with their caffeine use. The risks to sleep and alertness of regular caffeine use are greatly underestimated by both the general population and physicians.

http://www.ncbi.nlm.nih.gov/pubmed/17950009

Physiology And Behavior • December 2007

Additive effects of flavour-caffeine and flavour-flavour pairings on liking for the smell and flavour of a novel drink

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Abstract

Previous research has established that caffeine consumption can reinforce changes in liking for caffeine-paired flavours, while pairing a novel flavour with a liked or dislike taste can also result in enduring changes in liking for the flavour. The present study examined how these two forms of flavour-learning interact. 72 habitual caffeine consumers who liked sweet tastes rated the odour and flavour of a novel tea drink before and after four training sessions where the flavour was paired with either 100 mg caffeine or placebo in one of three flavour contexts: added sweetness (aspartame), bitterness (quinine) or control. The liking for both the odour and flavour of the tea increased after pairing with caffeine regardless of flavour context, while pairing with bitterness reduced flavour liking regardless of the presence of caffeine. Pairing with quinine increased the rated bitterness of the tea odour, and reduced the rated sweetness of the tea flavour, post-training, independent of effects of caffeine. These data suggest that flavour-caffeine and flavour-flavour associations have additive effects on drink liking, while confirming that flavour-flavour associations can alter the immediate sensory experience of a flavour alone.

http://www.ncbi.nlm.nih.gov/pubmed/17675193

Physiology And Behavior • September 2004

How habitual caffeine consumption and dose influence flavour preference conditioning with caffeine

Tinley EM1, Durlach PJ, Yeomans MR.
Author information

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Abstract

This study investigated the effects of both habitual caffeine use and dose administered in determining the ability of caffeine to reinforce conditioned changes in flavour preference. Thirty overnight-withdrawn moderate caffeine consumers and 30 non or low-dose caffeine (non/low) consumers evaluated five novel-flavoured fruit teas. Subsequently, their median-rated tea was used in four ensuing conditioning sessions. Either placebo, 1 or 2 mg/kg of caffeine (n=10 consumers, 10 non/low consumers in each condition), was added to the target tea, and all five teas were reevaluated at a final tasting. Pleasantness ratings over the four conditioning sessions indicated that non/low consumers' liking increased for the noncaffeinated fruit tea with no change for the tea containing either 1 or 2 mg/kg of caffeine. Among consumers, pleasantness ratings tended to decrease for the noncaffeinated fruit tea but increased significantly at the 1-mg dose and showed a tendency to increase at the 2-mg dose. Similar effects were shown in the evaluations made before and after conditioning, with no change in the nonexposed drinks. These results show that 1.0 mg/kg of caffeine reinforces changes in flavour pleasantness in acutely withdrawn habitual consumers but not in nonconsumers or nondependent low-caffeine consumers, further endorsing the negative-reinforcement theory of conditioning with caffeine.

http://www.ncbi.nlm.nih.gov/pubmed/15276794

Appetite • August 2002

Effect of caffeine-deprivation on liking for a non-caffeinated drink

Author information

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Abstract

Liking for a novel non-caffeinated drink decreases when regular caffeine consumers are exposed repeatedly to that drink when caffeine-deprived; however, this dislike is not manifest if people are subsequently tested when not caffeine-deprived (Yeomans et al., 2000a). The present study investigated the basis for this effect, and in particular, whether the decrease in liking observed is specific to the drink flavour experienced during caffeine-deprivation. Twenty-four caffeine consumers evaluated five novel drinks (fruit teas) at pre-training. For each person, the drink with the median liking score was subsequently consumed mid-morning after 12 h caffeine-deprivation on four non-consecutive training days. Rated pleasantness of this drink decreased significantly over these four training days. Subjects subsequently re-evaluated all five drinks on a test day when half the consumers were given 100mg caffeine two hours prior to testing, with the remainder receiving placebo. The group who remained deprived continued to express depressed liking for the exposed (target) drink, compared to their pre-training rating of that drink. In contrast, rated pleasantness was not depressed compared to pre-training ratings in the group who had received caffeine prior to testing. Rated pleasantness of the four unexposed drinks was equivalent to pre-training ratings, for both groups, suggesting that the effect of exposure on ratings of the target drink was specific to that drink. As expected, there was some evidence of improved mood in the group receiving caffeine on the test day; but as it was only ratings of the target drink that differed across groups, the group difference cannot be attributed to general effects of mood on use of the rating scale. These data suggest that the reversal of acquired changes in liking for drinks when consumers are changed from a caffeine-deprived to an undeprived condition is best explained in terms of state-dependent learning, that is specific to the drink experienced during caffeine-deprivation.

http://www.ncbi.nlm.nih.gov/pubmed/12160563

Food Chemistry And Toxicology • September 2002

Effects of caffeine on human behavior

By A. Smith
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Abstract

"The literature suggests that the following effects on behavior of adult humans may occur when individuals consume moderate amounts of caffeine. (1) Caffeine increases alertness and reduces fatigue. This may be especially important in low arousal situations (e.g. working at night). (2) Caffeine improves performance on vigilance tasks and simple tasks that require sustained response. Again, these effects are often clearest when alertness is reduced, although there is evidence that benefits may still occur when the person is unimpaired. (3) Effects on more complex tasks are difficult to assess and probably involve interactions between the caffeine and other variables which increase alertness (e.g. personality and time of day). (4) In contrast to the effects of caffeine consumption, withdrawal of caffeine has few effects on performance. There is often an increase in negative mood following withdrawal of caffeine, but such effects may largely reflect the expectancies of the volunteers and the failure to conduct "blind" studies. (5) Regular caffeine usage appears to be beneficial, with higher users having better mental functioning. (6) Most people are very good at controlling their caffeine consumption to maximise the above positive effects. For example, the pattern of consumption over the day shows that caffeine is often consumed to increase alertness. Indeed, many people do not consume much caffeine later in the day since it is important not to be alert when one goes to sleep. In contrast to effects found from normal caffeine intake, there are reports that have demonstrated negative effects when very large amounts are given or sensitive groups (e.g. patients with anxiety disorders) were studied. In this context caffeine has been shown to increase anxiety and impair sleep. There is also some evidence that fine motor control may be impaired as a function of the increase in anxiety. Overall, the global picture that emerges depends on whether one focuses on effects that are likely to be present when caffeine is consumed in moderation by the majority of the population or on the effects found in extreme conditions. The evidence clearly shows that levels of caffeine consumed by most people have largely positive effects on behavior. Excessive consumption can lead to problems, especially in sensitive individuals."

http://www.ncbi.nlm.nih.gov/pubmed/12204388

Medical Journal Of Australia • May 2001

Caffeine-induced cardiac arrhythmia: an unrecognised danger of healthfood products

Author information

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Abstract

We describe a 25-year-old woman with pre-existing mitral valve prolapse who developed intractable ventricular fibrillation after consuming a “natural energy” guarana health drink containing a high concentration of caffeine. This case highlights the need for adequate labelling and regulation of such products.

http://www.ncbi.nlm.nih.gov/pubmed/11419773

Psychopharmacology (Berlin) • June 1998

Conditioned flavour preference negatively reinforced by caffeine in human volunteers

Author information

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Abstract

This study examined whether 100 mg caffeine could reinforce preference for the flavour of a novel drink in moderate caffeine users, both after overnight caffeine abstinence and 2 h after receiving 100 mg caffeine, using a two-stage between-groups procedure with 36 volunteers. In the first stage, liking for a test drink (fruit tea) was assessed at breakfast following overnight caffeine abstinence, with half the subjects receiving caffeine. Liking for the tea increased significantly over four trials for subjects receiving caffeine, and decreased significantly in those without caffeine. These effects were greatest in subjects who rated the drink as highly novel. In stage two, subjects evaluated a second drink (fruit-juice) 2 h after receiving the tea, and again half the subjects received caffeine Those subjects who received caffeine in stage two but not stage one showed a significant increase in liking for the fruit-juice over the 4 test days, whereas subjects who did not receive caffeine at either stage showed a progressive decrease in liking for this drink. In contrast, no significant change in liking for the fruit-juice was seen at stage two for subjects who had received caffeine in stage one, regardless of the presence or absence of caffeine at stage two. Caffeine at breakfast increased ratings of energetic and lively, and energetic ratings also increased following caffeine in the fruit-juice in subjects who had not had caffeine at breakfast. Overall, these data are consistent with a negative reinforcement model of caffeine reinforcement, and demonstrate further the utility of the conditioned flavour preference method for evaluating reinforcing effects of drugs in humans.

http://www.ncbi.nlm.nih.gov/pubmed/9676901

Behavior And Pharmacology • November 1998

Mood and psychomotor performance effects of the first, but not of subsequent, cup-of-coffee equivalent doses of caffeine consumed after overnight caffeine abstinence

Author information

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Abstract

Moderate caffeine consumers (n = 64, mean caffeine intake 453 mg/day) were deprived of caffeine overnight and semi-randomly allocated to four treatment groups, designated PPP, CPP, CCP and CCC, where P is placebo and C is caffeine (1.2 mg/kg, giving an amount of caffeine similar to that consumed in a serving of ground coffee). Caffeine or placebo (i.e. no caffeine) were administered double-blind in novel fruit juice drinks at 10:15, 11:30 and 13:00 h on the test day. Before (baseline), and 45 min after each of these times the participants completed a mood questionnaire and begun psychomotor performance tests lasting 25 min (1-min tapping task, and a long-duration simple reaction time task (SRT). Caffeine significantly increased energetic mood and improved psychomotor performance relative to placebo. Caffeine had particularly marked effects on SRT performance, ameliorating the slowing of performance with time on task and removing the post-lunch dip in performance. However, the three caffeine treatments, CPP, CCP and CCC, were equally effective. That is, mood and performance were improved to the same extent by one, two and three spaced doses (totalling 86, 172 and 258 mg) of caffeine. This result is consistent with previous findings indicating a flat dose-response relationship for the psychoactive effects of caffeine; and because of the adverse effects (e.g. fatigue) associated with overnight caffeine deprivation, it suggests that there is little net benefit to be gained from frequent caffeine use. At the very least, it appears that the psychostimulant effects of caffeine cannot on their own account for the typical pattern of consumption of caffeine-containing drinks.

http://www.ncbi.nlm.nih.gov/pubmed/9862086

“The authors conclude that caffeine potentiates the acute toxicity of both cocaine and amphetamine ...”

American Journal Of Emergency Medicine • May 1992

Potentiation of cocaine and d-amphetamine toxicity with caffeine

Author information

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Division of Emergency Medicine, University of California, Davis, School of Medicine

Abstract

The effect of caffeine when combined with cocaine or amphetamine was studied in rats. Animals were pretreated with intraperitoneal vehicle (normal saline [NS]) or caffeine 100 mg/kg, then challenged with intraperitoneal cocaine (0, 35, 50, 70, or 90 mg/kg) or intraperitoneal d-amphetamine (0, 15, 25, 35, or 42 mg/kg). Animal behavior, time to, and incidences of seizures and death were recorded. This dose of caffeine alone did not cause seizures or death. Caffeine pretreatment significantly increased the incidence of overt seizures induced by either cocaine or amphetamine. Caffeine increased the incidence of cocaine-induced death from 10% to 90% at the 70 mg/kg cocaine dose (P less than .01). Caffeine increased amphetamine-induced death from 0% to 80% at 15 mg/kg (P less than or equal to .01), 10% to 70% at 25 mg/kg (P less than or equal to .01), and 30% to 80% at 35 mg/kg (P less than or equal to .01). To investigate mechanisms, additional animals were pretreated with the adenosine agonist, 2-chloroadenosine (2.5 and 10 mg/kg), before being challenged with NS, 90 mg/kg cocaine, or 42 mg/kg amphetamine. Pretreatment with 2-chloroadenosine had no affect in reducing cocaine or amphetamine toxicity. Combination pretreatment with caffeine and 2-chloroadenosine potentiated cocaine toxicity. The phosphodiesterase inhibitor, pentoxifylline, did not potentiate cocaine toxicity. The authors conclude that caffeine potentiates the acute toxicity of both cocaine and amphetamine, and that the failure of 2-chloroadenosine to alter this suggests that the toxicity of the stimulants cocaine and amphetamine may be modulated by nonspecific rather than specific adenosine- or phosphodiesterase-induced mechanisms.

http://www.ncbi.nlm.nih.gov/pubmed/1586430

“More than 50% of the total mutagenic activity of coffee can be accounted for by the activity of methylglyoxal.”

Gan • Japanese Medical Journal • October 1982

Mutagenicity of methylglyoxal in coffee

Kasai H, Kumeno K, Yamaizumi Z, Nishimura S, Nagao M,
Fujita Y, Sugimura T, Nukaya H, Kosuge T.

Abstract

“Major carbonyl compounds from a extract of ground roasted coffee beans were identified as 5-hydroxymethylfurfural, acetol, glyoxal, methylglyoxal and diacetyl. Among these carbonyl compounds, methylglyoxal showed considerable mutagenic activity toward Salmonella typhimurium TA100 without S9 mix (around 100,000 revertants/mg). More than 50% of the total mutagenic activity of coffee can be accounted for by the activity of methylglyoxal.”

http://www.ncbi.nlm.nih.gov/pubmed/6762317

CHAPTER TWENTY-SIX

Fictive Kin

The Peer Review

The Navajo Indians never mention common substance in finding or invoking kinship ties or norms. Kinship is defined in terms of the acts of giving birth and sharing sustenance. The primary bond in the Navajo kinship system is the mother-child bond, and it is in this bond that the nature and meaning of kinship become clear. In Navajo culture, kinship means intense, diffuse, and enduring solidarity, and this solidarity is realized in actions and behavior befitting the cultural definitions of kinship solidarity. Just as a mother is one who gives life to her children through birth and sustains their life by providing them with loving care, assistance, protection, and sustenance, kinsmen are those who sustain each other's life by helping one another, protecting one another, and by the giving or sharing of food and other items of subsistence. Where this kind of solidarity exists, kinship exists; where it does not, there is no kinship. Fictive kinship appears necessary to human survival and is found most often in minority communities.

American Journal Of Orthopsychiatry • January 2016

Emergency shelter care utilization in child welfare: Who goes to shelter care? How long do they stay?

Author information

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Abstract

“Emergency shelter care for children entering foster care is widely used as a temporary first placement, despite its contraindications. However, little research has examined predictors of utilization (e.g., entry into care, length of stay in care). A sample of 123 children (ages 6-13) entering foster care was studied to explore the variables associated with an initial placement in shelter care versus kinship care and variables associated with children staying less than 30 days in the shelter versus 30 days or longer. After applying a classification tree analysis (CTA via Optimal Data Analysis), results indicated that variables across the child’s ecology--specifically the microsystem, mesosystem, and exosystem--were associated with increased emergency shelter utilization, including older age, entering as a dependency case, more relatives and fictive kin with barriers to involvement in the child’s life, and the child welfare agency serving the child. These results suggest that although emergency shelter care utilization may be determined by a complex interaction of variables across the child’s ecology, policy and programmatic attention to some of these risk factors might be effective in limiting utilization so that children can enter care with a more long-term, family-based placement.”

http://www.ncbi.nlm.nih.gov/pubmed/26569355

“High risk of metabolic syndrome is transmitted from fathers and mothers to sons and daughters. Our results suggest that this transmission is irrespective of the socioeconomic position and health behaviors of the offspring.”

International Journal Of Epidemiology • May 2016

The role of life-course socioeconomic and lifestyle factors in the intergenerational transmission of the metabolic syndrome: results from the LifeLines Cohort Study

Author information

Klijs B1, Angelini V2, Mierau JO2, Smidt N3.

Abstract

BACKGROUND

The risk of metabolic syndrome is associated between parents and offspring, but studies are inconsistent on differences by sex of parents and offspring. Our aim is to investigate to what extent metabolic syndrome present in fathers and mothers is associated with risk of metabolic syndrome in sons and daughters. Furthermore, we investigate to what extent these associations are explained by socioeconomic factors and health behaviours.

METHODS

We used data from the LifeLines Cohort Study (N=7239). Metabolic syndrome was defined according to the NCEP-ATPIII criteria. Logistic regression analyses were performed to investigate associations of metabolic syndrome present in parents with the risk of metabolic syndrome in offspring. Analyses were sequentially adjusted for: age and sex; childhood factors (socioeconomic position and parental smoking); and adult factors (education, income, smoking, physical activity, alcohol intake, and dietary factors).

RESULTS

Multivariate regression analysis adjusted for age and sex showed associations of the metabolic syndrome between father-son: odds ratio (OR) [95% confidence interval (CI)] 2.41 (1.93-3.00), father-daughter: OR (95% CI) 1.80 (1.39-2.33)), mother-son: OR (95% CI) 1.82 (1.44-2.29) and mother-daughter: OR (95% CI) 1.97 (1.52-2.55). Furthermore, each individual factor underlying the metabolic syndrome in parents was associated with metabolic syndrome in offspring, but not for all parent-offspring combinations. None of the parent-offspring associations was attenuated when adjusting for socioeconomic factors and health behaviours.

CONCLUSIONS

High risk of metabolic syndrome is transmitted from fathers and mothers to sons and daughters. Our results suggest that this transmission is irrespective of the socioeconomic position and health behaviours of the offspring.

http://www.ncbi.nlm.nih.gov/pubmed/27170762

Journal Of The American Medical Directors Association • October 2015

Institutional Bereavement Care for Fictive Kin: Staff Grief in CCRCs

Author information

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Abstract

PURPOSE

The purpose of this study was to explore approaches used by administrators to respond to grief and bereavement among staff after the death of a resident.

FINDINGS

Emergent themes suggest that LTC facilities have freedom in how to provide support for staff members, family members, and other residents after the death of a loved one. However, results show variations in methods for notifying staff of a resident's death, inclusion of direct care staff in caring for the deceased, providing memorial services, and offering grief/bereavement support. When speaking of the loss of a resident and ways to provide grief/bereavement support, only 3 of the 10 administrators discussed the importance of extending such services to the staff.

IMPLICATIONS

"Causes of staff burnout in the CCRC workplace is an unresolved issue. Research has shown that inadequate grief and bereavement support for staff contributes to factors associated with staff burnout and retention. Although administrators hold formal services after a resident has died, there are differences among facilities. It may be that organizations could improve bereavement services for staff."

http://www.ncbi.nlm.nih.gov/pubmed/26208900

Social Science Research • March 2014

Relationships of choice: can friendships or fictive kinships explain the race paradox in mental health?

Author information

By D.M. Mouzon

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Abstract

"African Americans typically exhibit similar or better mental health outcomes than whites, an unexpected pattern given their disproportionate exposure to psychosocial stressors. The "race paradox in mental health" has been attributed to presumed stronger social ties among blacks but there is scarce empirical research in this regard. Using data from the 2001-2003 National Survey of American Life (N=4086), I test whether more abundant and higher quality friendships and fictive kin relationships among African Americans (if they exist) account for the race paradox in mental health. I find few race differences in the quantity and quality of friendships and fictive kinships and these differences did not explain the race paradox in mental health. Future research should investigate other potential resilience mechanisms among African Americans to explain their relatively positive mental health outcomes."

http://www.ncbi.nlm.nih.gov/pubmed/24468432

Family Relationships • October 2013

Racial and Ethnic Differences in Extended Family, Friendship, Fictive Kin and Congregational Informal Support Networks

Robert Joseph Taylor, Ph.D., M.S.W., Linda M. Chatters, Ph.D.,
Amanda Toler Woodward, Ph.D., M.S.W., and Edna Brown, Ph.D., M.S.W.
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Abstract

"Involvement with kin and non kin is an essential component of daily life for the vast majority of Americans. Family and friendship support networks are important for coping with the ongoing stresses of daily life (e.g. Benin & Keith, 1995), providing a place to live when confronting homelessness (Taylor, Chatters & Celious 2003), and in coping with physical and mental health problems (Cohen, Underwood & Gottlieb, 2000; Lincoln, 2000). This study explores differences between African Americans, non-Hispanic Whites and Caribbean Blacks (Black Caribbeans) on several measures of family, friendship, fictive kin and religious congregation-based informal support networks, using data from the National Survey of American Life. The literature review begins with a discussion of the family solidarity model as the theoretical perspective framing our analysis of kin and non-kin relations and social support. This is followed by a review of research findings on Black-White differences in family and non-kin support networks and a review of available information on informal support networks within the Caribbean Black population in the United States. This section concludes with a description of the focus and goals of the present investigation."

Full text, graphs, charts and 47 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4116141/

Community Medicine • July 2014

The collective voice: Legitimation strategies in focus group discussions with nurses in municipal palliative care for older people in Sweden

Rahm H, Andersson M, Edberg AK.

Abstract

“This paper explores focus group discussions of registered nurses in municipal palliative care for older people, using data collected by researchers with an interest in health sciences. The linguistically based discourse analyis builds on a combination of Bakhtinian notions of dialogicity, the Other and addressivity, the use of quotations, and also van Leeuwen’s framework for legitimation in discourse. The aim is to investigate strategies of addressing and legitimizing palliative care. Three types of narrative are discerned: the cautionary tale, fictionalization of professional experiences and the enactment of a fictive dialogue. The other professions involved (physicians, assistant nurses) are positioned as the Other as a means of legitimizing the perspectives of the registered nurses. As the patients and their next of kin are the objects of professional activities, the notion of the Third (connecting to the Other) is proposed. The objectification is a manifestation of commitment with routinized and professional distance to the patients.”

http://www.ncbi.nlm.nih.gov/pubmed/26596124

Journal Of The National Black Nurses Association • December 2014

Non-Biological (Fictive Kin and Othermothers): Embracing the Need for a Culturally Appropriate Pedigree Nomenclature in African-American Families

Author information

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Abstract

"Although the Family Health History (FHH) is the most cost-effective tool in the stratification of disease risk, it is not designed to collect information from non-biological family members (NBFM). Significant NBFM, defined as "fictive kin and othermothers," tend to play a major role in the transmission of culture, health promotion, and decision-making; yet, their influence cannot be captured using the standard FHH. Participants attending the National Black Nurses Association (NBNA) 2012 genetic workshop were divided into groups to role-play FHH. All participants (N = 50) indicated difficulties with the standard FHH, ranking collection of sensitive data as the number 1 challenge. Consequently, a new symbol was developed with support from NBNA genetics workshop participants. Having such a symbol affords an opportunity for inclusion of all NBFM to help guide risk-specific recommendations for disease management, prevention, and health promotion of common chronic diseases. This report will describe the process, presentation, and adoption of the symbol."

Full text, graphs, charts and 35 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4847537/

“The study provides support for the idea that the creation of fictive kin is a form of substitution for absent family members and shows that older adults in the Netherlands are active agents in the construction of their family network.”

Journal Of Gerontology Series B • Psychological Sciences And Social Sciences • September 2013

Just like family: fictive kin relationships in the Netherlands

By M. Voorpostel

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Abstract

OBJECTIVES

This study examined the extent to which older adults in the Netherlands include a nonrelative as part of their family (create fictive kin), and whether this process is similar in other age groups. It assessed the importance of absence of close family ties and the experience of divorce in the family network for the creation of fictive kin.

METHOD

Using data from the Netherlands Kinship Panel Study, logistic regression models for the different age groups tested the importance of absence of primary family relationships and the experience of divorce in the family among three age groups (18-40, 41-60, 61-79, N = 6,571).

RESULTS

Prevalence of fictive kin relationships was higher in older age groups. Both the absence of close family relationships and the experience of divorce within the family were related to having fictive kin, although the latter was only found in the youngest age group. For older adults never having married, being widowed or divorced were important predictors of having fictive kin relationships.

DISCUSSION

The study provides support for the idea that the creation of fictive kin is a form of substitution for absent family members and shows that older adults in the Netherlands are active agents in the construction of their family network.

http://www.ncbi.nlm.nih.gov/pubmed/23689999

Journal Of Transcultural Nursing • April 2012

Compadrazgo: a literature review

Author information

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Abstract

“Compadrazgo, “coparenthood,” is a traditional ritual fictive kinship system that provides a network of mutually supportive relationships in the Mexican American culture. A literature search of CINAHL, Medline, PsychoInfo, and Web of Science was used to identify peer-reviewed journals and original sources. Keywords included comadre, compadrazgo, fictive kin, social support, Mexican, and Mexican American. Additional resources were identified through a focused review of references. Findings from this study indicate knowledge about compadrazgo, is limited to the social organization, historical practices, and a preliminary description of the compadres role. Minimal information is available about the relationship between compadrazgo, and health, and variations in roles and responsibilities of compadrazgo, participants. Frequency of enactment of compadrazgo, responsibilities and barriers to the enactment of social support by compadres remain unknown. Variations in practice have not been explored. Nursing implication include the recommended ways that compadrazgo, can be encouraged or promoted in patient care.”

http://www.ncbi.nlm.nih.gov/pubmed/22267550

Qualitative Health Research • April 2011

Alternative families in recovery: fictive kin relationships among residents of sober living homes

Author information

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kevinheslin@cdrewu.edu

Abstract

“Sober living homes are group residences for people attempting to maintain abstinence from alcohol and drugs in a mutually supportive setting. Residents typically develop strong psychological and economic ties and have been referred to as “alternative families,” thus evoking the anthropological concept of fictive kinship. We analyzed data from seven focus groups with sober living home residents to assess the prevalence and functions of fictive kinship in these settings. Results suggest that residents created kinship by exchanging various types of support, and by incorporating other residents into existing family relationships, particularly in homes where there were children. Residents perceived fictive kin as more supportive than actual kin, encouraging them toward greater individuation, in contrast with family backgrounds that were sometimes described as stifling. These accounts of the therapeutic qualities of fictive kin in sober living homes could inform the work of fair housing advocates and other community stakeholders.”

http://www.ncbi.nlm.nih.gov/pubmed/20952602

Clinical Psychology (New York) • September 2011

Sister Circles as a Culturally Relevant Intervention for Anxious African American Women

Author information

Neal-Barnett A1, Stadulis R, Murray M, Payne MR, Thomas A, Salley BB.

Kent State University

Abstract

"Research on anxiety treatment with African American women reveals a need to develop interventions that address factors relevant to their lives. Such factors include feelings of isolation, multiple roles undertaken by Black women, and faith. A recurrent theme across treatment studies is the importance of having support from other Black women. Sister circles are support groups that build upon existing friendships, fictive kin networks, and the sense of community found among African Americans females. Sister circles appear to offer many of the components Black women desire in an anxiety intervention. In this article, we explore sister circles as an intervention for anxious African American women. Culturally-infused aspects from our sister circle work with middle-class African American women are presented. Further research is needed."

Full text, anxiety action plan and 42 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3212099/

“Evidence from this analysis provides support for hypotheses predicted by identity theory, highlights the importance of examining giving and receiving support net of the other, and suggests that it is often better for the well-being of older adults to give than to receive.”

Journal Of Gerontology, Series B, Psychological Sciences And Social Sciences • May 2010

Is it better to give or to receive? Social support and the well-being of older adults

Author information

By P.A. Thomas
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Abstract

OBJECTIVES

This study examines the separate effects of several dimensions of giving and receiving social support on the well-being of older adults, with hypotheses guided by identity theory.

METHODS

Data derive from the Social Networks in Adult Life survey, a national probability sample of older adults (N = 689). Ordinary least squares regression was used to examine the impact of total support, size of support network, number of types of support, and types of alter support relationships-both given and received-on well-being.

RESULTS

Providing support to others is beneficial to older adults' well-being, as illustrated in the relatively strong, positive associations of total support given, the number of types of support given, and support given to friends and children on well-being. Receiving support was less important to well-being except when received from a spouse or sibling.

CONCLUSION

Evidence from this analysis provides support for hypotheses predicted by identity theory, highlights the importance of examining giving and receiving support net of the other, and suggests that it is often better for the well-being of older adults to give than to receive.

http://www.ncbi.nlm.nih.gov/pubmed/20028952

American Journal Of Preventive Medicine • June 2009
Centers For Disease Control And Prevention

Family Health History Still an Important Tool for Clinical and Public Health Practice, but Knowledge Gaps Remain

(This website is archived for historical purposes and is no longer being maintained or updated)

CDC addresses public health implications of the findings and recommendations just released by a multidisciplinary panel of the Family History State-of-the-Science Conference hosted by the National Institutes of Health in Bethesda, Maryland, on August 24-25, 2009.

Although the scope of this conference was limited to primary care, and the panel's findings and recommendations targeted the research community, the conference's impact will likely be felt beyond these boundaries. As a partner in this conference and given our long-held support for the use of family history in public health, CDC's Office of Public Health Genomics addresses the following potential implications of this conference for public health efforts conducted by CDC and its partners.

Family History and Clinical Utility for Single Gene Disorders

Advances in family history and genetics research have helped to establish the role of family history in the diagnosis and management of single-gene (Mendelian) disorders. Although these disorders are individually rare, collectively they present a significant public health issue, particularly among children. The Family History State-of-the-Science Conference did not include single gene disorders; however, in this area of medicine, the utility of family history in clinical settings and for individuals and their families has been demonstrated for many disorders. Still, we do not know the extent to which family history applications have been translated into clinical practice. This gap highlights a potentially important public health need for providing valid and useful genetic services to various communities, particularly those that are underserved.

Family History and Risk Assessment for Common Chronic Diseases

Most common human diseases are caused by complex interactions between a person's genes, behaviors, and environmental exposures. Although there have been major scientific advances in understanding the behavioral causes (e.g., diet, smoking, and physical activity) of several chronic diseases, advances on the genetic causes of these diseases have been slower. Family history includes the genes, behaviors, and environmental exposures that relatives share in common. Research on the use of family history to assess disease risk has been inadequate, as has research on family history use in public health interventions for common diseases. Thus, family history, so far, has limited documented clinical utility in assessing the risk and targeting interventions for these diseases. However, family history, alone or in combination with other risk factors, increases the risk for common diseases, such as heart disease, stroke, diabetes, and various cancers, much more than genetic variants, alone or in combination, can predict. The familial risk often shows a dose-response effect. That is, the more close relatives a person has with a particular disease and the earlier their ages of diagnosis, the greater that person's risk of also developing the same disease. Research on translating family history applications for risk assessment and disease prevention into clinical and public health practice is just beginning.

The panel pointed out numerous research efforts that are needed. The panel and others proposed the ACCE framework for evaluating the analytical validity, the clinical validity, the clinical utility, and the ethical, legal, and social aspects of using family history to prevent disease and improve the health of populations. Some research in this area is already under way. For example, CDC is collaborating with three universities to conduct a randomized controlled clinical trial to evaluate the clinical utility of Family Healthware™ as a risk assessment tool for six common diseases (breast, ovarian, and colorectal cancer, diabetes, stroke, and heart disease). The methods and some results of this clinical trial have been published, but more is on the way.1-3

Family History Risk Assessment Tool

Family history has been and will continue to be a core component of clinical and public health practice. Although the panel pointed out the lack of evidence on the effectiveness of the many applications and uses of family history, they did not recommend against the collection and use of this information for common diseases. Existing tools, such as the My Family Health Portrait from the U.S. Surgeon General, is helping to facilitate the collection and use of family history by individuals and in clinical and public health settings. This information can still inform clinical encounters with patients and public health surveillance efforts in programs involving common chronic diseases in populations. However, users need to be aware that there are significant gaps in applying our knowledge of family history to common diseases. The specific recommendations that emerged from this conference are a good first step in paving the way for addressing these gaps.

1. Yoon PW, Scheuner MT, Jorgensen C, Khoury MJ. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. Prev Chronic Dis. 2009 Jan;6(1):A33. Epub 2008 Dec 15.
2. Wang C, O'Neill SM, Rothrock N, Gramling R, et al. Comparison of risk perceptions and beliefs across common chronic diseases. Prev med. 2009 Feb;48(2):197-202.
3. O'Neill SM, Rubinstein WS, Wang C, Yoon PW, et al. Familial risk for common diseases in primary care: the Family Healthware Impact Trial. Am J Prev Med. 2009 Jun;36(6):506-14.

www.cdc.gov/genomics/famhistory/famhist_2009-10_findings.htm

Journal Of Gerontology, Series B, Psychological Sciences And Social Sciences • November 2009

Social network types and subjective well-being in Chinese older adults

Author information

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Abstract

“The study examined social network types in a sample of 1,005 older Chinese adults in Hong Kong and the networks’ relations to subjective well-being. Given the nature of kinship in Chinese society, we broke down social support provision by closeness of blood ties (immediate kin, distant kin, and non-kin). Using K-means cluster analysis, we identified 5 network types: diverse, friend focused, restricted, family focused, and distant family. The latter was characterized by few immediate kin but mostly distant kin. Diverse and family-focused networks were most beneficial to well-being, whereas restricted networks were least. Distant family networks were associated with only marginally lower well-being than family-focused networks and were comparable to friend-focused networks. Results suggested the importance of the extended family in support provision for Chinese older adults, especially in the absence of immediate kin and friends. Implications of the present findings for other cultural groups are discussed.”

http://www.ncbi.nlm.nih.gov/pubmed/19820232

Healthcare And Social Work • August 2008

Developing a culturally responsive breast cancer screening promotion with Native Hawaiian women in churches

Author information

By L. S. Ka'opua

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Abstract

"This article presents findings from research to develop the promotional component of a breast cancer screening program for Native Hawaiian women associated with historically Hawaiian churches in medically underserved communities. The literature on adherence to health recommendations and health promotions marketing guided inquiry on screening influences. Focus groups and individual interviews patterned on the culturally familiar practice of talk story were conducted with 60 Hawaiian women recruited through religious and social organizations. Text data were analyzed with an incremental process involving content analysis and Airhihenbuwa's PEN-3 model. Key informants and senior colleagues reviewed preliminary findings to ensure accuracy of interpretation. Findings reflect collectivist values at the intersection of indigenous Hawaiian culture and religiosity. Inclusion of messages that encourage holistic health across the intergenerational continuum of extended family and fictive kin, reinforcement from spiritual leaders, and testimonials of cancer survivors and family members may facilitate Hawaiian women's screening intent."

Full text with 34 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938766/

Health & Social Work • November 2008

The impact of kin and fictive kin relationships on the mental health of black adult children of alcoholics

By J.C. Hall

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Abstract

"The purpose of this qualitative study was to examine how kin and fictive kinship relationships help to ameliorate or buffer responses to parental alcoholism and the breakdown in parenting. This qualitative study investigated coping responses developed by college students, who self-identified as adult children of alcoholics (ACOAs) who lived with an alcoholic parent or caregiver. In-depth interviews and follow-up participant checks were used. A descriptive model was developed describing conditions that affected the development of positive self-esteem, the phenomena that arose from those conditions, the context that influenced strategy development, the intervening conditions that influenced strategy development, and the consequences of those strategies. Subcategories of each component of the descriptive model are identified and illustrated by narrative data in relation to the ACOAs' psychological well-being. Implications for research, policy, and practice are discussed."

http://www.ncbi.nlm.nih.gov/pubmed/19070273

Journal Of Gerontological Nursing • November 2008

Day-to-day care: the interplay of CNAs' views of residents & nursing home environments

Author information

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Abstract

"This qualitative study identified certified nursing assistants' (CNAs') perspectives of nursing home residents and how these perspectives translate into care practices. Data included observations of and interviews with 27 CNAs in three dissimilar nursing homes. All participants were people of color, and all but 3 were immigrants. CNAs constructed three views of residents: as fictive kin, as a commodity, and as an autonomous person. Although individual CNAs held one primary view of residents in general, select residents were viewed from an alternative perspective, resulting in variations in care practices. These findings suggest that such distinctions, in tandem with structural, organizational, and cultural differences in nursing homes, present opportunities for nursing leadership to affect the visible, everyday practice of nursing CNAs. To target interventions, further research is needed on how CNAs come to differentially view residents and how these differences influence CNAs' care relationships with residents."

http://www.ncbi.nlm.nih.gov/pubmed/19024427

Journal Of Health And Social Policy • July 2006

Child Only Kinship Care Cases: The Unintended Consequences of TANF Policies for Families Who Have Health Problems and Disabilities

Author information

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Abstract

"The passage of the Personal Responsibility Work Opportunities Reconciliation Act (PRWORA) in 1996 changed the way America sought to help its most vulnerable citizens. The Temporary Assistance for Needy Families (TANF) legislation required families to work first. Many families with young children found the stringent requirements of TANF too restrictive for their needs. In this study a number of TANF customers were either physically ill or suffered mental health problems thus preventing them from finding suitable employment. Additionally they may have children who have health problems, which preclude the parent from work activity. Faced with time limits these families may rely on relatives or fictive kin to assume the responsibility of receiving TANF grants for the children so that they may avoid sanctions and possible loss of support for their children. These arrangements are called child-only cases. Given that poverty is related to neglect and neglect may result in out of home placement, these children are at risk for child welfare intervention. Child welfare systems look to kin to assume the responsibility of child rearing to reduce the number of children especially African American children who enter care. However, TANF and informal arrangements for kin to take care of children result in substantially less money for families. An evaluation of TANF is needed to determine if this legislation provides an adequate system for caring for needy families and children."

http://www.ncbi.nlm.nih.gov/pubmed/17855238

“From 2000 to 2004, the prevalence of severe poverty increased sharply while the proportion of Americans in higher income tiers diminished. These trends have broad societal implications. Likely health consequences include a higher prevalence of chronic illnesses, more frequent and severe disease complications, and increased demands and costs for healthcare services. Adverse effects on children warrant special concern. The growth in the number of Americans living in poverty calls for the re-examination of policies enacted in recent years to foster economic progress.”

American Journal Of Preventive Medicine • October 2006

The rising prevalence of severe poverty in America: a growing threat to public health

Author information

Woolf SH1, Johnson RE, Geiger HJ.

Abstract

BACKGROUND

The U.S. poverty rate has increased since 2000, but the depth of poverty experienced by Americans has been inadequately studied. Of particular concern is whether severe poverty is increasing, a trend that would carry important public health implications.

METHODS

Income-to-poverty (I/P) ratios and income deficits/surpluses were examined for the 1990-2004 period. The severely poor, moderately poor, and near-poor were classified as those with I/P ratios of less than 0.5, 0.5 to 1.0, or 1.0 to 2.0, respectively. Income deficits/surpluses were classified relative to the poverty threshold as Tier I (deficit Dollars 8000 or more), Tier II (deficit or surplus less than Dollars 8000), or Tier III (surplus more than Dollars 8000). Odds ratios for severe poverty and Tier I were also calculated.

RESULTS

Severe poverty increased between 2000 and 2004-those with I/P ratios of less than 0.5 grew by 20%, and Tier I grew by 45% to 55%-while the prevalence of higher levels of income diminished. The population in severe poverty was over-represented by children (odds ratio [OR] = 1.69, confidence interval [CI] = 1.63-1.75), African Americans (OR = 2.84, CI = 2.74-2.95), and Hispanics (OR = 1.64, CI = 1.58-1.71).

CONCLUSIONS

From 2000 to 2004, the prevalence of severe poverty increased sharply while the proportion of Americans in higher income tiers diminished. These trends have broad societal implications. Likely health consequences include a higher prevalence of chronic illnesses, more frequent and severe disease complications, and increased demands and costs for healthcare services. Adverse effects on children warrant special concern. The growth in the number of Americans living in poverty calls for the re-examination of policies enacted in recent years to foster economic progress.

http://www.ncbi.nlm.nih.gov/pubmed/16979459

Journal Of Gerontological Nursing • February 2005

Fictive kin: friends as family supporting older adults as they age

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Abstract

“Assessing social support or social capital is receiving renewed attention in health care. A search of the nursing literature revealed limited attention to a potential resource in the care of older adults—fictive kin. Transdisciplinary searches indicated that “fictive kin” or “chosen kin” are increasingly important as family size shrinks and older adults live longer lives. Fictive kin are common across cultural groups and some have designated special names for these quasi-family members. The purpose of this article is to advance the concept of fictive kin as a resource for older adults and to provide strategies to promote engagement of fictive kin in health care planning by nurses.”

http://www.ncbi.nlm.nih.gov/pubmed/15756983

Journal Of Developmental Behavior In Pediatrics • June 2005

The physical, developmental, and mental health needs of young children in child welfare by initial placement type

Author information
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Abstract

"The American Academy of Pediatrics recommends comprehensive assessments for children entering foster care. These children may be placed with biological parents, kin, or in nonrelative foster care. It is not known whether health-related needs differ by placement. Chart abstractions were conducted of child welfare and medical records of 1542 children, ages 3 months to 5 years 11 months, admitted to San Diego's sole emergency shelter/receiving facility from April 1, 1998, through June 30, 1999, for investigation of alleged maltreatment. Children were discharged to three placement types: biological parents (28.5%), kinship caregivers (28.4%), or nonrelative foster parents (43.1%). Overall, 86.7% of children studied demonstrated physical, developmental, or mental health needs, with more than half displaying two or more problems. More than half of the children had a "Suspect" score on the Denver-II; 70.3% of children with "Suspect" scores were found to have delay on a developmental evaluation. Almost one tenth of the sample were diagnosed with one or more mental health conditions. Few differences were found for physical, developmental, or mental health concerns by placement. Results suggest that young children placed with biological parents or in kinship care have similar needs to those of children placed with foster parents. This study confirms the importance of comprehensive assessments for young children removed from their homes, regardless of placement. It also illustrates a need for standardized assessment criteria, particularly for developmental and mental health status, and for collaborative care models for all young children entering the child welfare system, regardless of their placement following investigation."

Full text, graphs, charts and 54 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1550710/

Medical Clinics Of North America • July 2005

Health-related disparities: influence of environmental factors

By K. Olden and S. L. White

Abstract

Racial disparities in health cannot be explained solely on the basis of poverty, access to health care, behavior, or environmental factors. Their complex etiology is dependent on interactions between all these factors plus genetics. Scientists have been slow to consider genetics as a risk factor because genetic polymorphisms tend to be more variable within a race than between races. Now that studies are demonstrating the existence of racial differences in allelic frequencies for multiple genes affecting a single biologic mechanism, the present argument for a significant genetic role in contributing to health disparities is gaining support. Individuals vary, often significantly, in their response to environmental agents. This variability provides a high "background noise" when scientists examine human populations to identify environmental links to disease. This variability often masks important environmental contributors to disease risk and is a major impediment to efforts to investigate the causes of diseases.Fortunately, investments in the various genome projects have led to the development of tools and databases that can be used to help identify the genetic variations in environmental response genes that can lead to such wide differences in disease susceptibility. NIEHS developed the environ-mental genome project to catalog these genetic variants (polymorphisms)and to identify the ones that play a major role in human susceptibility to environmental agents. This information is being used in epidemiologic studies to pinpoint environmental contributors to disease better. The research summarized in this article is critically important for tying genetics and the environment to health disparities, and for the development of a rational approach to gauge environmental threats. Common variants in genes play pivotal roles in determining if or when illness or death result from exposure to drugs or environmental xenobiotics. Most common variants exist in all human populations, but their frequency can vary substantially,rendering individuals or groups more or less susceptible to particular environmental exposures. Such findings are consistent with the highly publicized analogy, "genetics loads the gun, but the environment pulls the trigger." That is, one can inherit the genetic predisposition to develop a disease but will do so only if or when exposed to the environmental trigger. Poor people have approximately the same genetic makeup as everyone else,but they have the unfortunate experience of living and working in environments containing multiple and high levels of carcinogens or other toxicants capable of interacting with susceptibility genes to cause disease.Furthermore, certain disadvantaged ethnic groups may have a higher incidence of certain susceptible genes that render them more vulnerable to adverse effects of the environments they inhabit. For both of these reasons,much of the nation's disease burden could likely be reduced through better environmental protection practices, especially in low-income and minority communities. Of the many implications of polymorphisms and frequency variations for public health and the practice of medicine, however, none is more urgent than the choice of drugs in therapy. Using such knowledge,randomized trials have identified race-specific drug response differences between blacks and whites [42].To date, most knowledge of the health effects of environmental factors is derived from studies of single agents. The reality, though, is that environmental contributions to health disparities are mostly from multiple agents. These simultaneous exposures to multiple risk factors, which may accumulate or interact synergistically, remain to be fully explained and defined.Finally, health disparity is a significant public health problem that cannot be solved using "business as usual" approaches for funding and priority setting. The current emphasis on basic and clinical research at the exclusion of public health and the social sciences does not provide the interdisciplinary research teams necessary to address such a complex problem as health disparities. Although the poor will always be with us, their health could be greatly improved if social, environmental, and genetic scientists could find ways to collaborate and develop more insightful and relevant ways to address the health of disadvantaged communities.

http://www.ncbi.nlm.nih.gov/pubmed/15925646

Care Management Journals • Spring 2003

Intercultural collaboration: an approach to long-term care for urban American Indians

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Abstract

"Most long term care of older urban American Indians is provided in the community by family, extended family, or fictive kin, and American Indians are rarely found in long term care facilities. An approach to American Indian elderly requires some understanding of Indian ways in order to be effective therapeutically and acceptable to the older Indian. Multiple interviews, a focus group, and a survey conducted in an urban Indian community revealed the consistent perception by American Indian elderly and their families that health care providers lacked information, understanding, and respect for Indian culture."

http://www.ncbi.nlm.nih.gov/pubmed/14502878

“These processes use personal choices as well as immediate needs to expand the basis of relatedness beyond blood and marriage. Thus the supportive capacities of networks increase in order to serve a potentially vulnerable population.”

Journal Of Gerontology • Series B • Psychological Sciences And Social Sciences • November 1999

Fictive kin among oldest old African Americans in the San Francisco Bay area

Author information

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Abstract

OBJECTIVES

The purpose here is to identify those processes that account for the more active and supportive kinship networks among Black oldest old than found among their White age peers.

METHODS

Focused interviews were conducted with 122 Blacks 85 years and older. Both open-ended and semistructured questions were asked in order to determine how Blacks defined family and kinship membership, their expectations for kin, and the desired levels of reciprocity.

FINDINGS

A content analysis of the responses indicated that Blacks defined the boundaries of their families flexibly so as to include fictive kin, and they upgraded more distant kin into the status of primary kin. They also emphasized the importance of collateral relatives so as to expand the size of the network.

DISCUSSION

These processes use personal choices as well as immediate needs to expand the basis of relatedness beyond blood and marriage. Thus the supportive capacities of networks increase in order to serve a potentially vulnerable population.

http://www.ncbi.nlm.nih.gov/pubmed/10625972

British Journal Of Medicine And Psychology • December 1998

Evolutionary kinship therapy: basic principles and treatment implications

Author information

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Abstract

"The idiom of kinship is a powerful one that stretches across many levels of social behaviour (van den Berghe, 1979), and Daly, Salmon & Wilson (1997) recently outlined the basic principles of a comprehensive, evolution-based kinship psychology. Their approach merges traditional kinship theory, Hamilton's inclusive fitness model and the broader realm of evolutionary psychology into an exciting and provocative call to arms. They address biological, psychological (viz. fictive kinship) and kin-like levels of analysis, and they argue for a relationship-specific kinship psychology that deals with the particular demands of being a mother, father, mate, offspring or grandparent. Our particular approach to kinship psychology has focused primarily on the distinction between biological kinship and psychological kinship (Bailey, 1988; Bailey & Wood, 1993; Nava & Bailey, 1991), and more recently on the role of kin-like relations in psychotherapy and other social contexts (Bailey, 1997a; Wood, 1997). The kin-like category is especially noteworthy in modern industrialized countries where acquaintance-ships and stranger-to-stranger interactions often predominate over biological and psychological kinships."

http://www.ncbi.nlm.nih.gov/pubmed/9875959

Gerontologist • December 1990

Families and networks among older inner-city blacks

Author information

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Abstract

“These research findings compare the support networks of inner-city blacks and whites, 65 years and older, who were selected from hospital medical clinics. Both blacks and whites who are in need of help use formal supports. Blacks, however, have more active support networks than do whites despite the low incidence of support from spouses and children. These social resources result from mechanisms in black families that expand network membership through the creation of fictive kin.”

http://www.ncbi.nlm.nih.gov/pubmed/2286330

CHAPTER TWENTY-SEVEN

Azodicarbonamide & Semicarbazide

The Peer Review

AZODICARBONAMIDE

Searches under the term azodicarbonamide leads to a total of 75 peer reviewed reports [1], leading to a paucity of evidence to report. However, workplace studies are plentiful and there are still reports based on human consumption or exposure to azodicarbonamide. Azodicarbonamide is a sneaky little devil. Its breakdown products and the chemicals it promotes are the real instigators of the problems related to human consumption of or exposure to azodicarbonamide.

1. PubMed Searched March 24th using "Azodicarbonamide," "Azodicarbonamide Food Additive" and "Azodicarbonamide Toxicity" and all searches yielded the same or a portion of the 75 peer reviewed reports that resulted from the original search:

http://www.ncbi.nlm.nih.gov/pubmed/?term=Azodicarbonamide

SEMICARBAZIDE

Semicarbazide has been shown to be formed in heat-treated flour containing Azodicarbonamide as well as breads made from Azodicarbonamide-treated flour and Semicarbazide is not a necessarily safe chemical for us to be consuming on a regular, daily, long-term basis based on the peer review that follows.

There are several additional chemicals discussed that are related to the metabolism of Azodicarbonamide that are also harmful to the human species in various systems and organs.

Azodicarbonamide occurs naturally in bread manufacturing and it's breakdown products also occur naturally as a result of heating in the baking process. This is a controversial chemical, banned in some countries and not others.

Azodicarbonamide Lined Food Container Caps

FULL LINER **WITHOUT LINER** **CIRCULAR RING LINER**

“In man, the increased Semicarbazide-sensitive amine oxidase (SSAO) activity detected in osteoarthritic patients may trigger hypertrophy and cartilage degeneration.”

Osteoarthritis And Cartilage • February 2016

Expression of the semicarbazide-sensitive amine oxidase in articular cartilage: its role in terminal differentiation of chondrocytes in rat and human

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Abstract

OBJECTIVE

Semicarbazide-sensitive amine oxidase (SSAO) catalyzes the oxidation of primary amines into ammonia and reactive species (hydrogen peroxide, aldehydes). It is highly expressed in mammalian tissues, especially in vascular smooth muscle cells and adipocytes, where it plays a role in cell differentiation and glucose transport. The study aims at characterizing the expression and the activity of SSAO in rat and human articular cartilage of the knee, and to investigate its potential role in chondrocyte terminal differentiation.

DESIGN

SSAO expression was examined by immunohistochemistry and western blot. Enzyme activity was measured using radiolabeled benzylamine as a substrate. Primary cell cultures of rat chondrocytes were treated for 21 days by a specific SSAO inhibitor, LJP 1586. Terminal chondrocyte differentiation markers were quantified by RT-qPCR. The basal and IL1ß-stimulated glucose transport was monitored by the entrance of 3[H]2-deoxyglucose in chondrocytes.

RESULTS

SSAO was expressed in chondrocytes of rat and human articular cartilage. SSAO expression was significantly enhanced during the hypertrophic differentiation of chondrocytes characterized by an increase in MMP13 and in alkaline phosphatase (ALP) expressions. SSAO inhibition delayed the late stage of chondrocyte differentiation without cell survival alteration and diminished the basal and IL1ß-stimulated glucose transport. Interestingly, SSAO activity was strongly increased in human osteoarthritic cartilage.

CONCLUSIONS

SSAO was expressed as an active form in rat and human cartilage. The results suggest the involvement of SSAO in rat chondrocyte terminal differentiation via a modulation of the glucose transport. In man, the increased SSAO activity detected in osteoarthritic patients may trigger hypertrophy and cartilage degeneration.

http://www.ncbi.nlm.nih.gov/pubmed/26851450

“... semicarbazide-sensitive amine oxidase inhibitors may be promising candidates for the prevention of chronic kidney disease in patients using Cisplatin to treat malignancy.”

Kidney International • November 2015

Interstitial renal fibrosis due to multiple cisplatin treatments is ameliorated by semicarbazide-sensitive amine oxidase inhibition

Author information

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Abstract

Elucidation of acute kidney diseases and disorders (AKD), including acute kidney injury (AKI), is important to prevent their progression to chronic kidney disease. Current animal AKI models are often too severe for use in evaluating human AKI. Therefore, new animal models of mild kidney injury are needed. Here a new clinically relevant animal model using multiple low doses of cisplatin (CP) was used to evaluate AKD. When 10 mg/kg CP was administered intraperitoneally once weekly for three times to L-type fatty acid-binding protein (L-FABP) transgenic mice, moderate renal interstitial fibrosis and tubule dilatation occurred, accompanied by brush-border loss. Urinary L-FABP, a promising biomarker of AKI, changed more drastically than blood urea nitrogen or creatinine. Preventing fibrosis in organs was also studied. Oral administration of a recently reported selective semicarbazide-sensitive amine oxidase inhibitor, PXS-4728A, for 1 week attenuated kidney injury and interstitial fibrosis compared with vehicle. Inhibition of renal lipid accumulation in semicarbazide-sensitive amine oxidase inhibitor-treated mice, together with reduced oxidative stress and L-FABP suppression in proximal tubules, suggested an anti-fibrotic effect of semicarbazide-sensitive amine oxidase inhibition in this CP-AKD model, a representative onco-nephrology. Thus, semicarbazide-sensitive amine oxidase inhibitors may be promising candidates for the prevention of chronic kidney disease in patients using CP to treat malignancy.

http://www.ncbi.nlm.nih.gov/pubmed/26535996

“... over time scientists gradually found that azodicarbonamide in sealed cans and flour could also lead to the generation of Semicarbazide. This discovery makes the study of Semicarbazide particularly interesting. At present, an increasing number of researchers are investigating the toxicity of Semicarbazide and developing more and better analytical methods for the determination of Semicarbazide.”

Food Additive Contamination Part A • Chemistry, Analysis, Control, Exposure And Risk Assessment • October 2014

Semicarbazide — from state-of-the-art analytical methods and exposure to toxicity: a review

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Abstract

This review assesses the state of the art concerning semicarbazide (SEM). Originally, SEM was primarily detected as a nitrofurazone veterinary metabolite, but over time scientists gradually found that azodicarbonamide in sealed cans and flour could also lead to the generation of SEM. This discovery makes the study of SEM particularly interesting. At present, an increasing number of researchers are investigating the toxicity of SEM and developing more and better analytical methods for the determination of SEM. In recent years, many researchers have focused on exposure from different foods, the public awareness of hazards and analytical detection methods for SEM in different foods. Although there have been significant achievements, these results have not been summarised in a review. The exposure from different foods, toxicity and methods of detection for SEM are comprehensively reviewed here. This review will provide not only others with a better understanding of SEM but also background information to facilitate future research.

http://www.ncbi.nlm.nih.gov/pubmed/25127068

“Therefore, we show, for the first time, alterations in hepatocellular expression of glucose and fructose transporters in chronic liver disease and provide evidence that the semicarbazide-sensitive amine oxidase activity of vascular adhesion protein-1 modifies hepatic glucose homeostasis and may contribute to patterns of glucose transporters expression in chronic disease.”

American Journal Of Physiology, Gastrointestinal Liver Physiology • December 2014

Dysregulated hepatic expression of glucose transporters in chronic disease: contribution of semicarbazide-sensitive amine oxidase to hepatic glucose uptake

Author information

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Abstract

Insulin resistance is common in patients with chronic liver disease (CLD). Serum levels of soluble vascular adhesion protein-1 (VAP-1) are also increased in these patients. The amine oxidase activity of VAP-1 stimulates glucose uptake via translocation of transporters to the cell membrane in adipocytes and smooth muscle cells. We aimed to document human hepatocellular expression of glucose transporters (GLUTs) and to determine if VAP-1 activity influences receptor expression and hepatic glucose uptake. Quantitative PCR and immunocytochemistry were used to study human liver tissue and cultured cells. We also used tissue slices from humans and VAP-1-deficient mice to assay glucose uptake and measure hepatocellular responses to stimulation. We report upregulation of GLUT1, -3, -5, -6, -7, -8, -9, -10, -11, -12, and -13 in CLD. VAP-1 expression and enzyme activity increased in disease, and provision of substrate to hepatic VAP-1 drives hepatic glucose uptake. This effect was sensitive to inhibition of VAP-1 and could be recapitulated by H2O2. VAP-1 activity also altered expression and subcellular localization of GLUT2, -4, -9, -10, and -13. Therefore, we show, for the first time, alterations in hepatocellular expression of glucose and fructose transporters in CLD and provide evidence that the semicarbazide-sensitive amine oxidase activity of VAP-1 modifies hepatic glucose homeostasis and may contribute to patterns of GLUT expression in chronic disease.

Full text, printer friendly version, photos, graphs, charts, with 62 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4269679/?report=printable

“These results showed that azodicarbonamide and its metabolites could be detected by the vibrational spectra technique, which might be applied as a powerful tool for the rapid detection on these species derived from agents added to flour.”

Spectrochimica Acta Part A Molecular And Biomolecular Spectroscopy • October 2013

Comparative studies by IR, Raman, and surface-enhanced Raman spectroscopy of azodicarbonamide, biurea and semicarbazide hydrochloride

Author information

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Abstract

Azodicarbonamide is widely applied in the food industry as a new flour gluten fortifier in China, Canada, the United States, and some other countries, whose metabolites of biurea and semicarbazide hydrochloride are reaction products during baking. In this study, IR, Raman and surface-enhanced Raman scattering (SERS) spectra of azodicarbonamide, biurea, and semicarbazide hydrochloride have been studied, and vibrational bands have been assigned on the basis of density functional theory (DFT) calculations. The calculated Raman spectra were in good agreement with experimental Raman spectra. The SERS method coupled with active gold substrates has also been applied for detection of the three chemicals with pure water as solvent, with the limit of detection of this method being as low as 10 μg/mL (less than 45 μg/mL). These results showed that azodicarbonamide and its metabolites could be detected by the vibrational spectra technique, which might be applied as a powerful tool for the rapid detection on these species derived from agents added to flour.

http://www.ncbi.nlm.nih.gov/pubmed/23751223

“Sensitivity analysis suggested that concentration of Semicarbazide in food is the most significant parameter governing human exposure via consumption of Semicarbazide-containing food.”

Journal Of Food Protection • September 2012

Semicarbazide in selected bird’s nest products

Author information

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Abstract

Currently, a number of food producers use hypochlorite to bleach food and inhibit the growth of bacteria, preserving the food. Because the presence of high amounts of nitrogen could result in the formation of semicarbazide (SEM), the bleaching process could be one of the predominant sources of SEM in food. To investigate this, we selected instant bottled bird’s nest as an example of a food that is bleached in its production. SEM was detected in 27 of 28 instant bottled bird’s nest samples. The levels of SEM detected mostly fell in the range of 5 to 50 µg/kg, which accounted for 75% of all samples measured. The SEM detected in the instant bottled bird’s nest was found to have originated neither from the use of the antimicrobial agent nitrofurazone nor from azodicarbonamide, which is used as a blowing agent in gaskets used to seal the metal lid of the bottle. Instead, it could have originated from the bleaching process used in the preparation of the nests. Additionally, human exposure to SEM via consumption of instant bottled bird’s nest for five subgroups of the population was estimated. Sensitivity analysis suggested that concentration of SEM in food is the most significant parameter governing human exposure via consumption of SEM-containing food.

http://www.ncbi.nlm.nih.gov/pubmed/22947474

Neurotoxicology • October 2012

Distribution and accumulation of caffeine in rat tissues and its inhibition on semicarbazide-sensitive amine oxidase

Author information

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Abstract

“Wistar rats were treated with caffeine or 2-bromoethylamine, the effect of caffeine on the activity of semicarbazide-sensitive amine oxidase (SSAO) in rat serum and tissues was studied using various LC-MS methods. Caffeine was found to present in all tissues after administration for 10 days and accumulated for 25 days. The level of caffeine was high in brain and liver, and the SSAO activity in all tissues was found to be inhibited by caffeine. As the concentration of caffeine increased, the SSAO activity decreased. The inhibition ratio was correlated to the levels of caffeine present. We presume that caffeine may treat with SSAO activity associated diseases.”

http://www.ncbi.nlm.nih.gov/pubmed/22841599

“For dough physical properties and dough consistency during mixing, the best response was found when ... Azodicarbonamide [was] between 110 and 170 ppm.”

International Journal Of Food Sciences & Nutrition • June 2011

Use of sodium stearoyl lactylate and azodicarbonamide in wheat flour breads with added pea flour

Author information

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1. Instituto de Tecnología de Alimentos, Facultad de Ingeniería Química, Universidad Nacional del LitoralSanta Fe, Argentina

Abstract

Different amounts of sodium stearoyl lactylate (SSL) (X(1)) and azodicarbonamide (ADA) (X(2)) were analyzed to measure their effect on breadmaking using wheat flour with incorporation of pea flour (Pisum sativum) to the dough. The objective of the present work was to optimize the physical properties of dough (Y(1)Y(2)Y(3)Y(4)), the dough consistency during mixing (Y(5)Y(6)) and the baking performance (Y(7)Y(8)Y(9)). A central composite design and second-order models for Y(i) were employed. For dough physical properties and dough consistency during mixing, the best response was found when SSL varied between 0.5 and 1.5% and ADA between 110 and 170 ppm. For responses concerning the baking performance, better values for specific volume, crumb texture scores and bread score were obtained using SSL between 0.9 and 1.4% and ADA between 50 and 80 ppm. It is concluded that for baking with wheat flour replaced at about 10% with inactivated pea flour it should be advised to use SSL at levels close to 1% with ADA between 50 and 80 ppm.

http://www.ncbi.nlm.nih.gov/pubmed/21306191

“The concentration of semicarbazide in all types of flour products is higher than that in flour, and the concentration of semicarbazide in outside of flour products is slightly higher than that in the inside. As the problem of food safety hazard aggravates daily, we should be more concerned about food security and human health.”

Journal Of Agricultural And Food Chemistry • September 2011

Assessment of the determination of azodicarbonamide and its decomposition product semicarbazide: investigation of variation in flour and flour products

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Abstract

Azodicarbonamide, as a bleaching agent and improving agent, is a permitted food additive in certain countries and can be determined by high-performance liquid chromatography. However, it partially degrades with the heat of processing to form trace amounts of semicarbazide, which shows carcinogenicity and also has been shown to cause tumors. The concentration of semicarbazide in azodicarbonamide-treated flour was determined by isotope dilution ((13)C, (15)N(2)-semicarbazide) liquid chromatography electrospray tandem mass spectrometry (LC-MS/MS). The quantification was obtained utilizing the homologous internal standard. The limits of detection were 1 mg/kg for azodicarbonamide and 0.5 × 10(-3) mg/kg for semicarbazide. The rates of recovery were 82.3-103.1% for azodicarbonamide and 72.4-116.5% for semicarbazide. This study prepared four different types of flour products to investigate the variation of semicarbazide. The concentration of semicarbazide in all types of flour products is higher than that in flour, and the concentration of semicarbazide in outside of flour products is slightly higher than that in the inside. As the problem of food safety hazard aggravates daily, we should be more concerned about food security and human health.

http://www.ncbi.nlm.nih.gov/pubmed/21786817

“... oral administration of 50, 100 and 150 mg kg(-1) b.w. of Semicarbazide showed a statistically significant effect in micronucleus frequencies on Wistar rats’ bone marrow polychromatic erythrocytes ...”

Food And Chemical Toxicology • January 2010

Evaluation of genotoxic effects of semicarbazide on cultured human lymphocytes and rat bone marrow

Author information

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Abstract

Semicarbazide (SEM) belongs to the hydrazine family of chemicals, some members of which are known to possess carcinogenic potential. Information on the potential hazard of SEM itself is incomplete and the possibility that it is genotoxic cannot be ruled out. SEM is widely used as a residue marker for the banned veterinary drug nitrofurazone. Also, it occurs as a break-down product of azodicarbonamide (ADC), a chemical used as a flour treatment. Furthermore, it may form as a reaction product of hypochlorite action on food additives. In the present study, we investigated the possible genotoxic effects of SEM with respect to the following cytogenetic endpoints: (1) in vitro micronucleus (MN) formation and sister-chromatid exchange (SCE) induction in human lymphocytes and (2) in vivo micronucleus induction on rat bone marrow polychromatic erythrocytes (PCEs). Comparing MN and SCE frequencies on control and examined concentrations (0.5, 2.5, 5, 10 and 20 microg ml(-1)) did not reveal statistically significant differences except, marginally, the highest concentration (20 microg ml(-1)) in SCE analysis. On the other hand, oral administration of 50, 100 and 150 mg kg(-1) b.w. of SEM showed a statistically significant effect in MN frequencies on Wistar rats’ bone marrow PCEs, with no dose-response pattern.

http://www.ncbi.nlm.nih.gov/pubmed/19819287

Chemical & Biological Interactions • January 2010

The food contaminant semicarbazide acts as an endocrine disrupter: Evidence from an integrated in vivo/in vitro approach

Author information

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De Angelis G, Testai E, Mastrangelo S, Evandri MG, Bolle P, Lorenzetti S.

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Abstract

Semicarbazide (SEM) is a by-product of the blowing agent azodicarbonamide, present in glass jar-sealed foodstuffs mainly baby foods. The pleiotropic in vivo SEM toxicological effects suggested to explore its possible role as endocrine modulator. Endocrine effects of SEM were assessed in vivo in male and female rats after oral administration for 28 days at 0, 40, 75, 140mg/kg bw pro die during the juvenile period. Vaginal opening and preputial separation were recorded. Concentration of sex steroid in blood, the ex vivo hepatic aromatase activity and testosterone catabolism were detected. The in vitro approach to test SEM role as (anti)estrogen or N-methyl-d-aspartate receptors (NMDARs)-(anti)agonist included different assays: yeast estrogenicity, MCF-7 proliferation, stimulation of the alkaline phosphatase activity in Ishikawa cells and LNCaP-based NMDAR interference assay. In vivo SEM-treated female rats showed delayed vaginal opening at all tested doses, whereas in males preputial separation was anticipated at SEM 40 and 75mg/kg and delayed at 140mg/kg, the latter effect probably due to the significantly decreased body weight gain seen at the higher dose in both sexes. Serum estrogen levels were dose-dependently reduced in treated females, whereas dehydrotestosterone serum levels were also decreased but a clear dose-response was not evidenced. Testosterone catabolism was altered in a gender-related way, aromatase activity was increased in treated males at 75 and 140mg/kg and in females in all dose groups. In the three estradiol-competitive assays, SEM showed a weak anti-estrogenic activity, whereas in the LNCaP-based NMDAR interference assay SEM activity resembled MK-801 antagonist effect. SEM appeared to act as an endocrine disrupter showing multiple and gender specific mechanisms of action(s). A possible cascade-mechanism of SEM on reproductive signalling pathways may be hypothesized. Such in vivo-in vitro approach appeared to be an useful tool to highlight SEM activity on endocrine homeostasis.

http://www.ncbi.nlm.nih.gov/pubmed/19788891

“Semicarbazide (SEM) is a by-product of the blowing agent azodicarbonamide, present in glass jar-sealed foodstuffs mainly baby foods. Concentration of sex steroid in blood, the ex vivo hepatic aromatase activity and testosterone catabolism were detected. In vivo SEM-treated female rats showed delayed vaginal opening at all tested doses, whereas in males preputial separation was anticipated at SEM 40 and 75mg/kg and delayed at 140mg/kg, the latter effect probably due to the significantly decreased body weight gain seen at the higher dose in both sexes. Serum estrogen levels were dose-dependently reduced in treated females ... In the three estradiol-competitive assays, SEM showed a weak anti-estrogenic activity, whereas in the LNCaP-based NMDAR interference assay SEM activity resembled MK-801 antagonist effect. SEM appeared to act as an endocrine disrupter showing multiple and gender specific mechanisms of action(s).”

Food And Chemical Toxicology • February 2009

Effects of the food contaminant semicarbazide following oral administration in juvenile Sprague-Dawley rats

Author information

Maranghi F1, Tassinari R, Lagatta V, Moracci G, Macrì C, Eusepi A, Di Virgilio A, Scattoni ML, Calamandrei G.

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Abstract

Semicarbazide (SEM) is an azodicarbonamide by-product present in glass jar packaged foods including babyfoods, in bleaching steps and flour treatment. Experimental data showed SEM acting as osteolathyrogen agent, but few toxicological data are available in susceptible life-stages. This study aimed to evaluate effects of SEM oral administration for 28 days at 0, 40, 75, 140 mg/kg bw day during the juvenile period in Sprague-Dawley rats. Histopatological examinations of: epiphyseal cartilage - potential target of SEM lathyrogen action - testes, ovary, uterus, thyroid, thymus, spleen, adrenals, representative of the main developing organs relevant to juvenile toxicity, and neurobehavioural tests in males, were performed. Mortality at high and mid dose levels and significantly decreased body weight gain were observed in males even at the lowest dose. Lack of mineralization in cartilage at all dose levels was present. Marked alterations of spontaneous motor and exploratory behaviours were evident even at 40 mg/kg. Histological alterations were observed in all tissues; thyroid and ovary effects were present also at 40 mg/kg. The present study indicate that the NOAEL in juvenile rats is lower than 40 mg/kg for SEM oral administration. SEM administration during juvenile period exerted pleiotropic effects and further studies are suggested to elucidate mechanisms.

http://www.ncbi.nlm.nih.gov/pubmed/19110027

“Semicarbazide (SEM) is an azodicarbonamide by-product present in glass jar packaged foods including babyfoods, in bleaching steps and flour treatment. Experimental data showed SEM acting as osteolathyrogen agent, but few toxicological data are available in susceptible life-stages. Mortality at high and mid dose levels and significantly decreased body weight gain were observed in males even at the lowest dose. Lack of mineralization in cartilage at all dose levels was present. Marked alterations of spontaneous motor and exploratory behaviours were evident even at 40 mg/kg. Histological alterations were observed in all tissues; thyroid and ovary effects were present also at 40 mg/kg.”

Journal Of Agricultural Food Chemistry • March 2008

Semicarbazide formation in flour and bread

Author information

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http://www.ncbi.nlm.nih.gov/pubmed/18303820

Abstract

“Azodicarbonamide, an approved food additive, is commonly used as a flour additive and dough conditioner in the United States and Canada. A number of researchers have clearly established a link between the use of azodicarbonamide and semicarbazide contamination in commercial bread products. However, all of these studies have primarily focused on the final baked product and have not extensively investigated the processing and conditions that affect the final semicarbazide levels. In this study, a previously developed method for measuring free semicarbazide in bread was applied to dough samples during the mixing and kneading process. Additionally, flour and bread samples were spiked with biurea or azodicarbonamide to help elucidate semicarbazide formation pathways. The results showed that semicarbazide was not formed as a byproduct of azodicarbonamide decomposition to biurea, which occurs upon the addition of water. Indeed, semicarbazide was not detected after room temperature or elevated temperature dough maturation, but only after baking. It was concluded that although azodicarbonamide is the initial starting material, semicarbazide formation in bread occurs through a stable intermediate, biurea.”

BIUREA

Industry Synonyms • Other Names Biurea Is Known As Or Called

1 Biurea
2 Ureidourea
3 1,2-HYDRAZINEDICARBOXAMIDE
4 Bicarbamamide
5 Bicarbamimidic acid
6 110-21-4
7 Hydrazocarbonamide
8 Urea, ureido-
9 Hydrazodicarbonamide
10 Hydrazodicarboxamide
11 N,N'-Dicarbamoylhydrazine
12 hydrazine-1,2-dicarboxamide
13 Hydradicarbonamide
14 Pseudourea, 3-ureido-
15 (carbamoylamino)urea
16 Semicarbazide, 1-carbamoyl-
17 Formimidic acid, 1-semicarbazido-
18 N,N'-Biscarbamoylhydrazine
19 Ureidoureacarboxamide
20 Hydrazine, 1,2-dicarbamoyl-
21 Formamide, 1,1'-hydrazobis-
22 1,1-Hydrazoformamide
23 Semicarbazide, 1-(1-hydroxyformimidoyl)-
24 Hydrazinedicarboxylic acid diamide
25 NSC 1897
26 Hydrazinecarboximidic acid, 2-(aminocarbonyl)-
27 Hydrazine, 1,2-bis(aminocarbonyl)-
28 Bicarbamimidic acid (VAN)
29 1,1'-Hydrazobis(formamide)
30 CCRIS 5976
31 HSDB 5014
32 EINECS 203-747-2
33 AI3-28537
34 Hydrazodiformamide
35 Biscarbamoylhydrazine
36 Carbamoylsemicarbazide
37 Hydrazinedicarboxamide
38 AC1Q5JJY
39 Hydrazine,2-dicarbamoyl-
40 UNII-POJ4UOY01H
41 Formamide,1'-hydrazobis-
42 DSSTox_CID_4628
43 POJ4UOY01H
44 1-(aminocarbonylamino)urea
45 1,1'-Hydrazinebisformamide
46 AC1L1Q4I
47 DSSTox_RID_77474
48 DSSTox_GSID_24628
49 SCHEMBL21785
50 KSC177M6R
51 CHEMBL3188383
52 CTK0H7668
53 Hydrazine,2-bis(aminocarbonyl)-
54 NSC1897
55 MolPort-003-909-729
56 ULUZGMIUTMRARO-UHFFFAOYSA-N
57 KST-1B8739
58 NSC-1897
59 ZINC4284404
60 Tox21_300989
61 8704AC
62 AR-1B5992
63 LS-502
64 STL281876
65 ZINC04284404
66 AKOS005174048
67 MCULE-1306740070
68 NCGC00248246-01
69 NCGC00254891-01
70 AN-22591
71 CAS-110-21-4
72 CJ-11843
73 KB-48102
74 OR010932
75 OR172791
76 OR200778
77 OR200779
78 DB-040907
79 B0512
80 FT-0606465
81 R1547
82 ST50409446
83 A840149
84 Q-200731
85 I14-30123
86 3B1-000396
87 3B3-021744

BIUREA

Biurea is a chemical compound with the molecular formula C2H6N4O2. It is produced in food products containing azodicarbonamide, a common ingredient in bread flour, when they are cooked. Upon exposure, biurea is rapidly eliminated from the body through excretion. Biurea is produced from urea and hydrazine. Its major use is as a chemical intermediate in the production of azodicarbonamide. Semicarbazide formation in bread occurs through the stable intermediate, biurea, in the gut.

Preferred IUPAC name: Hydrazine-1,2-dicarboxamide
Systematic IUPAC name: Carbamoylaminourea

FOR MORE INFORMATION ON BIUREA

PubChem, Open Chemistry Database, Biurea,
Last accessed November 22, 2015:

https://pubchem.ncbi.nlm.nih.gov/compound/8039#section=Top

“Most notably azodicarbonamide (ADC) has been implicated as an alternative source of semicarbazide. Azodicarbonamide is used in some countries as a dough conditioner at concentrations up to 45 mg kg(-1). The use of Azodicarbonamide-treated flour or dough in coated or breaded food products may generate false non-compliant results in the analytical method for nitrofurazone metabolites, which is currently in use. During the dough preparation process Azodicarbonamide is largely reduced to biurea, which can be considered as an appropriate marker residue of Azodicarbonamide. Thus far no methods have been published for the determination of biurea in food commodities.”

Analls Chim Acta • March 2007

The determination of biurea: a novel method to discriminate between nitrofurazone and azodicarbonamide use in food products

Author information

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Abstract

Recently doubts have arisen on the usefulness of semicarbazide as marker residue for the illegal use of the antibiotic nitrofurazone (NFZ) in aquaculture and poultry production. Most notably azodicarbonamide (ADC) has been implicated as an alternative source of semicarbazide. ADC is used in some countries as a dough conditioner at concentrations up to 45 mg kg(-1). The use of ADC-treated flour or dough in coated or breaded food products may generate false non-compliant results in the analytical method for nitrofurazone metabolites, which is currently in use. During the dough preparation process ADC is largely reduced to biurea, which can be considered as an appropriate marker residue of ADC. Thus far no methods have been published for the determination of biurea in food commodities. Due to its polar nature it is very difficult to generate sufficient retention on conventional C18 HPLC columns. With a TSK amide HILIC type column good retention was obtained. A straightforward extraction-dilution protocol was developed. Using a mixture of dimethyl formamide and water biurea was nearly quantitatively extracted from a variety of fresh, coated and processed products. Mass spectrometric detection was performed with positive electrospray ionisation. The sensitivity and selectivity of the mass spectrometer for biurea was very good, allowing detection at concentrations as low as 10 microg kg(-1). However, in some extracts severe ion suppression effects was observed. To overcome the implications of ion suppression on the quantitative performance of the method an isotopically-labelled biurea internal standard was synthesized and incorporated in the method. The method developed can be used effectively in nitrofurazone analysis to eliminate the risk of false non-compliant results due to the presence of azodicarbonamide-treated components in the food product.

http://www.ncbi.nlm.nih.gov/pubmed/17386736

“Semicarbazide (SEM), the marker residue for the banned nitrofuran veterinary antibiotic nitrofurazone (NFZ), has been detected regularly in foods—47% of recent nitrofuran EU Rapid Alertsinvolve Semicarbazide.”

Analytica Chimica Acta • May 2007

Enzyme immunoassay for semicarbazide—the nitrofuran metabolite and food contaminant

Author information

Cooper KM1, Samsonova JV, Plumpton L, Elliott CT, Kennedy DG.

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Abstract

Semicarbazide (SEM), the marker residue for the banned nitrofuran veterinary antibiotic nitrofurazone (NFZ), has been detected regularly in foods (47% of recent nitrofuran EU Rapid Alerts involve SEM). However, the validity of SEM as a definitive marker for NFZ has been undermined by SEM arising from other sources including azodicarbonamide, a plastics blowing agent and flour treatment additive. An inexpensive screening test for SEM in food matrices is needed--all SEM testing currently uses expensive LC-MS/MS instrumentation. We now report the first production of antibodies against derivatised SEM. A novel carboxyphenyl SEM derivative was used to raise a polyclonal antibody that has been incorporated into a semi-quantitative microtitre plate ELISA, validated according to the criteria set out in Commission Decision 2002/657/EC, for use with chicken muscle. The antibody is highly specific for derivatised SEM, cross-reactivity being 1.7% with NFZ and negligible with a wide range of other nitrofurans and poultry drugs. Samples are derivatised with o-nitrobenzaldehyde and simultaneously protease digested before extraction by cation exchange SPE. The ELISA has a SEM detection capability (CCbeta) of 0.25 microg kg(-1) when a threshold of 0.21 microg kg(-1) is applied to the selection of samples for confirmation (lowest observed 0.25 microg kg(-1) fortified sample, n=20), thus satisfying the EU nitrofurans’ minimum required performance limit of 1 microg kg(-1). NFZ-incurred muscles (12) containing SEM at 0.5-5.0 microg kg(-1) by LC-MS/MS, all screened positive by this ELISA protocol which is also applicable to egg and chicken liver.

http://www.ncbi.nlm.nih.gov/pubmed/17499072

GMS Krankenhaushygiene Interdisziplinar • September 2007

Virucidal agents in the eve of Manorapid Synergy

By A.S. Galabov
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Abstract

“Virucidal agents are chemical substances that attack and inactivate viral particles outside the cell (virions). In general this is accomplished by damaging their protein shells (capsid) or the substance penetrates the core itself, where it destroys the genetic material. Damage to the virion structure is also possible. These agents are used not only for traditional surface disinfection or sterilization of blood, blood products, and other medicinal products as well as in antiviral chemotherapy. They have also been used in recent times for inactivation of viruses in foodstuffs, detergents or cosmetics. Below is given an overview of the data currently available on the performance of these substances when used for the latter applications (cleaning and cosmetics).

These include:

hydrogen peroxide, hypochlorites, cupric and ferric ions, per-acidsethanol, parachlorometaxylenol in a sodium C14-16 olefin sulfonate, glutaraldehyde, quaternary ammonium salts, chlorhexidine and chlorhexidine gluconate, curdline sulphate, glycerol, lipids, azodicarbonamide, cicloxolone sodium, dichlorisocyanuric acid (sodium salt), benzalkonium salts, disulfate benzamides and benzisothiazolones, congo red, ascorbic acid, nonoxynol-9, para-aminobenzoic acid, bis(monosuccinamide) derivative of p,p’-bis(2-aminoethyl) diphenlyi-C60) (fullerene).merocyanine, benzoporphyrin derivative monoacid ring A, rose bengal, hypericin, hypocrellin A, anthraquinones extracted from plants, sulfonated anthraquinones and other anthraquinone derivatives, Gramicidine, Gossypol, Garlic (Allium Sativum) Extract And its components: ajoene, diallyl thiosulfinate (allicin), allyl methyl thioulfinate, methyl allyl thiosulfinate, extracts of ledium, motherworth, celandine, black currant, coaberry and bilberry, extract of Cordia salicifolia, steam distillate from Houttuynia cordata (Saururaceae) and its component, 5,6,7-trimethoxyflavone from Calicarpa japonica, isoscullarein (5,7,8,4’-tetrahydroxyflavone) from Scutellaria baikalensis and isoscutellarein-8-methylether, alkaloids and phytosteryl ester compounds.”

Full text with 44 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2831485/

“In some instances, concentrations of semicarbazide varied between batches of the same product, at times more than tenfold ...”

Food Additives And Contaminants • February 2006

Semicarbazide in Canadian bakery products

Author information

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Abstract

Levels of semicarbazide were determined by liquid chromatography-tandem mass spectrometry using isotope dilution ((13)C(15)N(2)-semicarbazide) methodology, and they were measured, after hydrolysis in 0.125 M hydrochloric acid and derivatization with 2-nitrobenzaldehyde, as a sum of free and bound semicarbazide. Levels of semicarbazide in 11 bakery products, which were sampled at three time intervals from the same source, varied from not detected (<1ng g(-1)) to 560 ng g(-1). In some instances, concentrations of semicarbazide varied between batches of the same product, at times more than tenfold, suggesting that the addition of azodicarbonamide to the same product is not standardized in many baking establishments.

http://www.ncbi.nlm.nih.gov/pubmed/16449051

> “Levels of semicarbazide ranged from 10 to 1200 ppb in commercial bread products with azodicarbonamide listed among their ingredients.”

Journal Of Agricultural And Food Chemistry • June 2005

The determination of semicarbazide (N-aminourea) in commercial bread products by liquid chromatography-mass spectrometry

Author information

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Abstract

Recently, semicarbazide has been found in food in jars sealed with cap liners that were manufactured using azodicarbonamide as a blowing agent. These reports raised the concern that the use of azodicarbonamide-an approved dough conditioner-may result in semicarbazide residues in bread. To answer this question, a method based upon the previously reported liquid chromatography/tandem mass spectrometry determination of the semicarbazone of o-nitrobenzaldehyde was utilized. The method adopted for this work includes an extensive cleanup and reaction with o-nitrobenzaldehyde at pH 3.5, rather than with the widely used 0.1 M HCl, to form the semicarbazone derivative. A stable isotope dilution assay was used to determine the free semicarbazide present in the bread products. Levels of semicarbazide ranged from 10 to 1200 ppb in commercial bread products with azodicarbonamide listed among their ingredients.

http://www.ncbi.nlm.nih.gov/pubmed/15941299

MARKETING TO THE MASSES • SPORTING EVENTS

As fans cheered the World Cup in 2014, public health officials were questioning the placement of junk food marketing at such major sporting events, as governments grapple with a rising epidemic of obesity and related illnesses. In the UK alone, sales of unhealthy food and beverages tied to the televised games will reach $459 million, according to consumer research firm Webloyalty. Four years ago, during the first week of tournament play in the 2010 World Cup in South Africa, sales of chips and chocolate rose by 10 percent and 37 percent, respectively, compared to the same week the previous year, when there was no tournament. Likewise, other major televised sporting events drive sales of unhealthy foods with sales of sugary drinks increasing by 10 percent compared to the previous year.

Thiago Hérick de Sá, a nutritionist at the University of Sao Paulo in Brazil, says junk food marketers “represent a direct attack” on global efforts to stabilize the obesity epidemic through improvements in nutritional choices. Such marketing counters the effort by Latin American governments in particular to fight obesity, he wrote in a letter published in The Lancet.

“The basic aim of any company is to sell their products or services and to profit,” de Sá told Medical News Today. “The sponsorship of major sporting events [by fast-food and sugary drink companies] is part of the company’s marketing strategy to achieve that aim, to encourage people, including children, to consume more of their products.” Deadly products in the longer term.

For this year’s tournament, FIFA has partnered with Coca-Cola, and gotten sponsorship from McDonald’s and Budweiser, among other makers of unhealthy foods and beverages, de Sá wrote in the letter published in The Lancet. For decades, these marketers have sought to associate unhealthy products with world-class athleticism, a message counter to the harsh biological realities of human life. An original, Coca-Cola was the first such company to engage in sports-related marketing, sponsoring the 1928 Olympics.

Susan Swithers, a professor in the Department of Health and Sciences at Purdue University, says children may be particularly affected by sports-related junk food marketing during major sporting events. “They see these messages everywhere and we know that children are more vulnerable to advertising messages than adults,” she told Medical News Today. “And for many kids, athletes are role models, so unhealthy foods get a boost in the eyes of children through their connection with events like the Olympics.” Critics of sports-related junk food marketing say the association between such products are an insult to our intelligence and for those less endowed, it should be a crime—either way.

Food Additives And Contaminants • September 2005

Safety assessment and risk-benefit analysis of the use of azodicarbonamide in baby food jar closure technology: putting trace levels of semicarbazide exposure into perspective—a review

Nestmann ER, Lynch BS, Musa-Veloso K, Goodfellow GH, Cheng E, Haighton LA, Lee-Brotherton VM.

Dr. E.R. NESTMANN & INTERTEK • A DUBIOUS CONNECTION

Intertek is a global leader in delivering expert scientific, toxicological, and regulatory services. They protect their customers' interests, helping them successfully meet regulatory obligations and bring products to market in a time-efficient and cost-effective manner. Their clients are industry leaders such as Candela, Carrefour, Citgo, ConocoPhillips, Kraft Foods, Heinz Foods, The Petroleum Authority of Thailand (PTT Oil), Unilever and more. Intertek works for the chemical food manufacturing industry to produce peer review that allows their clients poisonous, carcinogenic and mutagenic chemicals to be added to food. In other words, they massage the peer review to meet the needs of industry. This is generally referred to as lying. This peer reviewed report was authored by E. R. Nestmann for Cantox Health Sciences International, now known as Intertek. Dr. Nestmann has also been employed by the US government to produce peer reviewed literature to meet their needs as well. This report is just another biased report that reaches false conclusions. The false conclusion here being that infants ingestion of Semicarbazide and the toxicological effects of Semicarbazide are outweighed by the industry need to manufacture a cheap, cost effective bottle cap. What's one or two brain injured infants per every 21,000 when the bottle cap industries' profits are at stake?

Abstract

The discovery of trace levels of semicarbazide (SEM) in bottled foods (especially baby foods) led to a consideration of the safety of this hydrazine compound by regulatory agencies worldwide. Azodicarbonamide, which is used in the jar-sealing technology known as Press On-Twist Off (or Push-Twist/PT) closures for the formation of a hermetic, plastisol seal, partially degrades with the heat of processing to form trace amounts of SEM. This review has evaluated the potential toxicological risks of resulting exposure to SEM and also the benefit of the PT technology (with azodicarbonamide) in the context of possible microbial contamination. It also considers the potential impact on infant nutrition if parents come to the conclusion that commercial baby foods are unsafe. SEM shows limited genotoxicity in vitro that is largely prevented by the presence of mammalian metabolic enzymes. Negative results were found in vivo in DNA alkaline elution, unscheduled DNA synthesis and micronucleus assays. This pattern is in contrast to the genotoxic hydrazines that also have been shown to cause tumours. Carcinogenicity studies of SEM are of limited quality, show a questionable weak effect in mice at high doses, which are not relevant to human exposure at trace levels, and show no effect in the rat. The IARC has assigned SEM as Group 3, 'Not classifiable as to its carcinogenicity to humans'. Based on estimates of exposure to infants consuming baby foods (with the assumption of SEM levels at the 95th percentile of 20 ng g(-1) in all of the consumed 'ready-to-eat' foods) compared with a no observed adverse effect level (NOAEL) in developmental toxicity studies, the margin of safety is more than 21,000. Since the risk of an adverse effect is negligible, it is clear that any theoretical risk is outweighed by the benefits of continuing use of the PT closure (with azodicarbonamide blowing agent) to ensure both the microbial integrity and availability of commercial baby foods as a valuable source of infant nutrition.

http://www.ncbi.nlm.nih.gov/pubmed/16192074

“The results indicate that the compound azodicarbonamide was responsible for the source of the contaminant semicarbazide.”

Food Additives And Contaminants • January 2004

Implications of the use of semicarbazide as a metabolic target of nitrofurazone contamination in coated products

Author information

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Abstract

Data from the Brazilian Agricultural Ministry show that before the implementation of the Brazilian programme of nitrofuran control in February 2003, the cases of contamination of Brazilian chicken by nitrofurans were almost exclusively due to furaltadone. After May 2003, such cases decreased until no more reports of Brazilian chicken contamination with this nitrofuran were reported. Curiously, after April 2003, an increase was observed in the numbers of contaminated samples by semicarbazide, the target metabolite of nitrofurazone. Most Brazilian chicken found to be contaminated with semicarbazide has been covered with flour, salt and spices. For this reason, the authors' laboratory initialized a programme for tracing possible sources of food contamination by semicarbazide. After several semicarbazide positives in flour of controlled origin (results varying between 2.2 and 5.2 microg kg(-1)), the different additives used in the cereal industry as flour improvement agents were studied. The results indicate that the compound azodicarbonamide was responsible for the source of the contaminant semicarbazide.

http://www.ncbi.nlm.nih.gov/pubmed/14744681

Yonsei Medical Journal • April 2004

Occupational asthma due to azodicarbonamide

Author information

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Abstract

Azodicarbonamide is a low molecular weight foaming agent for plastics and rubbers. Azodicarbonamide can elicit acute and chronic health related problems due to its potential for pulmonary and cutaneous sensitization. Some cases of occupational asthma associated with exposure to azodicarbonamide have been reported, of which only a few cases were confirmed by specific inhalation challenges. Here, the first case of occupational asthma due to azodicarbonamide in Korea, in which the diagnosis was confirmed by specific inhalation challenge, is reported.

Full text PDF with graph and 17 references

http://www.eymj.org/Synapse/Data/PDFData/0069YMJ/ymj-45-325.pdf

The Analyst • March 2004

Semicarbazide is a minor thermal decomposition product of azodicarbonamide used in the gaskets of certain food jars

Author information

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Abstract

Evidence is presented for the first time showing that semicarbazide (SEM) is a minor thermal decomposition product of the blowing agent azodicarbonamide (ADC). A novel direct analytical method based on liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESIMS/MS) has been developed to determine SEM in foamed polyvinyl chloride (PVC) seals of metal lids, as well as in commercially available ADC. The direct LC-MS/MS method for gaskets entails extraction of the gaskets in hot water, addition of ((15)N(2)(13)C)-SEM as internal standard, and injection of an aliquot directly into the LC-MS system, achieving good sensitivity (S/N = 348 for 2 ng injected on-column) and monitoring three characteristic mass transitions (m/z 76-->31; 76 -->44; 76-->59). Semicarbazide can be detected in thermally treated ADC, reaching up to 0.93 mmol mol(-1) at 220 degrees C, as determined by the direct LC-MS/MS method. This new method is also compared to the classical derivatization method using 2-nitrobenzaldehyde (2-NBA) that is routinely employed to determine SEM as an indicator of the usage of the antimicrobial drug nitrofurazone, the use of which is not authorized in the European Union (EU). Both methods revealed proportional results, with approx. 3-fold higher levels recorded by the direct SEM approach, probably due to differences in the extraction procedures used. A limited survey of plastic seals from used press twist and twist-off metal lids on food jars (non-foamed and foamed) revealed levels of SEM ranging from 2 to 8689 microg kg(-1)(average = 1593 microg kg(-1), n= 57 determinations).

http://www.ncbi.nlm.nih.gov/pubmed/14978533

“Evidence is presented for the first time showing that semicarbazide (SEM) is a minor thermal decomposition product of the blowing agent azodicarbonamide (ADC). A limited survey of plastic seals from used press twist and twist-off metal lids on food jars (non-foamed and foamed) revealed levels of SEM ranging from

2 to 8,689

micrograms per kilogram(-1)

(average = 1,593 microg kg(-1) ...”

Journal Of Agricultural And Food Chemistry • September 2004

Semicarbazide formation in azodicarbonamide-treated flour: a model study

Author information

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Abstract

Semicarbazide was previously found in foods that were in contact with rubber gaskets foamed at high temperatures with a blowing agent azodicarbonamide. Because azodicarbonamide is an approved flour additive in certain countries, we set out to ascertain if semicarbazide is formed during the baking process from flours containing that additive. The levels of semicarbazide in baking flour treated with azodicarbonamide and bread baked from such flours were determined by isotope dilution (13C15N2-semicarbazide) liquid chromatography electrospray tandem mass spectrometry (LC-MS/MS). The samples were homogenized with HCl, extracted with n-pentane, derivatized with 2-nitrobenzaldehyde, and the derivative was extracted with ethyl acetate. After solvent exchange to 10% acetonitrile in water containing 0.1% acetic acid, the samples were analyzed using a 2.1 mm x 150 mm C18 column eluted with 2 mM ammonium formate in water/methanol (40:60). Semicarbazide was formed during the dry heating of commercial azodicarbonamide-containing flours at temperatures of 150-200 degrees C reaching levels of 0.2 mg/kg. Similar levels of semicarbazide were found in the crusts of breads made from azodicarbonamide-treated flour.

http://www.ncbi.nlm.nih.gov/pubmed/15373416

“This study has shown that semicarbazide induces DNA damage in the presence of Cu(II) through the formation of hydrogen peroxide and Cu(I). In addition, semicarbazide-derived free radicals participate in DNA damage. DNA damage induced by these reactive species may be relevant to the carcinogenicity of semicarbazide.”

Mutation Research • April 2003

Carcinogenic semicarbazide induces sequence-specific DNA damage through the generation of reactive oxygen species and the derived organic radicals

Author information

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Radioisotope Center, Mie University School of Medicine. Edobashi 2-174, Tsu, Mie 514-8507, Japan

Abstract

Semicarbazide, a hydrazine derivative, is carcinogenic to mice but shows no or little mutagenicity in the Salmonella-microsome test. To clarify whether or not the genotoxic mechanism contributes to the non-mutagenic carcinogenicity of semicarbazide, we investigated DNA damage induced by semicarbazide using 32P-5’-end-labeled DNA fragments obtained from the c-Ha-ras-1 protooncogene and the p53 tumor suppressor gene. Semicarbazide caused DNA damage frequently at the thymine and cytosine residues in the presence of Cu(II). Catalase and bathocuproine partially inhibited DNA damage, suggesting that hydrogen peroxide plus Cu(I) participates in DNA damage. When a high concentration of semicarbazide was used in the presence of catalase, DNA damage was induced, especially at G in 5’-AG and slightly at 5’-G in GG and GGG sequences. An electron paramagnetic resonance (EPR) spectroscopic study has confirmed that the reaction of semicarbazide with Cu(II) produces carbamoyl radicals (z.rad;CONH(2)), possibly generated via the nitrogen-centered radicals of semicarbazide. Azodicarbonamide also produced carbamoyl radicals and induced DNA damage frequently at 5’-G in GG and GGG sequences, suggesting that carbamoyl radicals participate in this sequence-specific DNA damage by semicarbazide. On the basis of our previous reports, we consider that the sequence-specific DNA damage at G in 5’-AG in the present study is due to the nitrogen-centered radicals. This study has shown that semicarbazide induces DNA damage in the presence of Cu(II) through the formation of hydrogen peroxide and Cu(I). In addition, semicarbazide-derived free radicals participate in DNA damage. DNA damage induced by these reactive species may be relevant to the carcinogenicity of semicarbazide.

http://www.ncbi.nlm.nih.gov/pubmed/12694749

“Thus, in vitro azodicarbonamide decreases the intracellular pool of deoxyribonucleotide and thymidine phosphorylation.”

Biochemical Pharmacology • August 2002

Ribonucleotide reductase and thymidine phosphorylation: two potential targets of azodicarbonamide

Author information

Fagny C1, Vandevelde M, Svoboda M, Robberecht P.,
Department of Biochemistry and Nutrition. Faculty of Medicine, Université Libre de Bruxelles, Brussels, Belgium

Abstract

Azodicarbonamide tested as an anti-HIV agent was reported to expulse zinc from viral zinc-cysteine factors and to inhibit calcium mobilization machinery. It has structural analogy with hydroxyurea that inhibits ribonucleotide reductase and could also act on this target. Azodicarbonamide was therefore tested for its capacity to modulate deoxyribonucleotides triphosphate pools alone or in combination with other agents in the lymphoblastic SUP-T1 cell line susceptible to HIV infection. The deoxyribonucleotides triphosphate were evaluated by an enzymatic assay using sequenase. Two hours exposure of SUP-T1 cells to 100 microM azodicarbonamide induced a 50% reduction of each deoxyribonucleotide triphosphate. Among other inhibitors of nucleotide metabolism (hydroxyurea, methotrexate and thymidine), hydroxyurea only reproduces the effect of azodicarbonamide. This suggests, but does not demonstrate directly, that azodicarbonamide inhibits ribonucleotide reductase activity. The combination of azodicarbonamide with each of these inhibitors affected particularly the dCTP pool. During this study it was also suggested that azodicarbonamide could interfere with thymidine phosphorylation. Thymidine phosphorylating activity was measured with 3H-thymidine as substrate. In acellular preparations, azodicarbonamide also non-competitively inhibits thymidine phosphorylating activity. This effect was not reproduced by hydroxyurea. Thus, in vitro azodicarbonamide decreases the intracellular pool of deoxyribonucleotide and thymidine phosphorylation.

http://www.ncbi.nlm.nih.gov/pubmed/12147296

“Azodicarbonamide was administered at escalating doses concomitantly with current antiviral therapy during a 3-month open-label period in patients with advanced AIDS and documented virological failure. After 3 months, patients were randomized in a double-blind placebo-controlled withdrawal, Azodicarbonamide being given at the highest tolerated dosage.”

AIDS • January 2001

Phase I/II dose escalation and randomized withdrawal study with add-on azodicarbonamide in patients failing on current antiretroviral therapy

Author information
Goebel FD1, Hemmer R, Schmit JC, Bogner JR, de Clercq E, Witvrouw M, Pannecouque C, Valeyev R, Vandevelde M, Margery H, Tassignon JP.

Abstract

BACKGROUND
Azodicarbonamide (ADA), a HIV-1 zinc finger inhibitor, targets a new step in viral replication and cell infectivity.
OBJECTIVE
A first phase I/II clinical study of ADA.
METHODS
ADA was administered at escalating doses concomitantly with current antiviral therapy during a 3-month open-label period in patients with advanced AIDS and documented virological failure. After 3 months, patients were randomized in a double-blind placebo-controlled withdrawal, ADA being given at the highest tolerated dosage.
RESULTS
Fifteen patients with advanced disease failing on combined antiretroviral therapy, 75% of them with proven phenotypic resistance, had a median baseline CD4 cell count of 85 x 10(6) cells/l, CD4/CD8 cell ratio of 0.09 and median plasma RNA viral load of 4.2 log10 copies/ml. Tolerance to ADA was dose dependent and some patients developed nephrolithiasis, glucose intolerance or showed an ADA-related cytotoxicity towards CD4 cells at higher dosages. No patient died during the study period. ADA increased CD4 cell percentage, increased the CD4/CD8 cell ratio and decreased plasma RNA viral load from baseline. At the end of the double-blind period, the ADA group, but not the placebo group, showed a significant response ($P < 0.05$). No phenotypic resistance to ADA was observed. Overall, 3/11 patients (27%) had consistent viral load reductions > 0.5 log10 copies/ml compared with baseline and 5/ 11 (45%) showed a CD4 cell recovery from baseline > 33%. In responders, ADA induced a median peak increase in CD4 cell percentage change from baseline of 65% (range 47-243%), and viral load decrease of 1.04 log10 copies/ml (range 0.52-1.23).

CONCLUSIONS

The maximal tolerated dosage of ADA appears to be 2 g (three times daily). This study provides safety results that will allow larger clinical trials to confirm the preliminary efficacy data.

http://www.ncbi.nlm.nih.gov/pubmed/11192866

“In conclusion, the immunosuppressive action of azodicarbonamide is mainly related to its effect on the calcium mobilization machinery and is synergistic with that of calcineurin inhibitors.”

Clinical Immunology • July 2001

Azodicarbonamide as a new T cell immunosuppressant: synergy with cyclosporin A

Author information

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Abstract

We recently demonstrated that azodicarbonamide is an immunosuppressive compound that inhibits calcium mobilization in T lymphocytes. In this study, we show that azodicarbonamide prevents the progression of human CD4+ T lymphocytes into the G1 phase of the cell cycle, inhibits their blastogenesis, down-regulates their membrane expression of CD25 and CD69, and decreases their transcription of cytokine genes. Addition of the calcium ionophore A23187 completely restores T cell proliferation in the presence of azodicarbonamide. Furthermore, azodicarbonamide synergizes with cyclosporin A to inhibit CD4+ T cell proliferation. In conclusion, the immunosuppressive action of azodicarbonamide is mainly related to its effect on the calcium mobilization machinery and is synergistic with that of calcineurin inhibitors.

http://www.ncbi.nlm.nih.gov/pubmed/11414742

“Azodicarbonamide was recently identified as a new anti-HIV agent ...
In addition to its anti-HIV properties, azodicarbonamide is a new immunosuppressive agent that might have therapeutic applications in T cell-mediated inflammatory disorders.”

Nature Medicine • August 1999

Azodicarbonamide inhibits T-cell responses in vitro and in vivo

Author information
Tassignon J1, Ismaili J, Le Moine A, Van Laethem F, Leo O, Vandevelde M, Goldman M.
Laboratory of Experimental Immunology, Université Libre de Bruxelles, Brussels, Belgium

Abstract
Azodicarbonamide was recently identified as a new anti-HIV agent that targets the zinc finger domains of the HIV-1 NCp7 nucleocapsid protein. Here, we demonstrate that azodicarbonamide inhibits in a dose-dependent manner the responses of purified human CD4+ T lymphocytes stimulated either by monoclonal antibodies against CD3 and CD28 or by allogeneic dendritic cells. These suppressive effects involve a direct action on the calcium mobilization machinery, as azodicarbonamide strongly inhibited the calcium influx induced either by antibodies against CD3 and CD28 or the chemokine RANTES, as well as by thapsigargin, an activator of depletion-activated calcium channels. In vivo, administration of azodicarbonamide into mice blunted their response to polyclonal T-cell activation induced by the injection of monoclonal antibody against CD3 and resulted in delayed rejection of skin allografts. In addition to its anti-HIV properties, azodicarbonamide is a new immunosuppressive agent that might have therapeutic applications in T cell-mediated inflammatory disorders.

http://www.ncbi.nlm.nih.gov/pubmed/10426321

“Bottled beers contained even higher amounts of ethyl carbamate (up to 14.7 micrograms/l) and this was considered to be due to the use of azodicarbonamide as a blowing agent in the beer bottle cap liners. It is understood that modifications to the liner have led to reduced concentrations in bottled beers produced more recently. Toasting bread led to increases of between three- and eight-fold in ethyl carbamate concentrations ranging from 3.5 to 33.8 micrograms/kg on a wet weight basis. Analysis of the data indicated that commercial bread samples which indicated the use of azodicarbonamide as a flour improver showed statistically significant increases in ethyl carbamate concentrations. The mean increase for treated bread over untreated bread was 66%.”

Food Additives And Contaminants • January 1997

The contribution of azodicarbonamide to ethyl carbamate formation in bread and beer

Author information

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Abstract

Data on ethyl carbamate concentrations in beers purchased and analysed between 1988 and 1990 are presented. The concentrations in draught beers were uniformly below the detection limit of 1 microgram/l. Canned beers contained rather more ethyl carbamate (up to 2.5 micrograms/l) which is considered to be due to their longer shelf-life and higher alcohol content (in some cases). Bottled beers contained even higher amounts of ethyl carbamate (up to 14.7 micrograms/l) and this was considered to be due to the use of azodicarbonamide as a blowing agent in the beer bottle cap liners. It is understood that modifications to the liner have led to reduced concentrations in bottled beers produced more recently. A survey of bread samples and related cereal products such as rusks, French toasts and pitta bread indicated typical ethyl carbamate concentrations between < 0.4 and 4.5 micrograms/kg. Toasting bread led to increases of between three- and eight-fold in ethyl carbamate concentrations ranging from 3.5 to 33.8 micrograms/kg on a wet weight basis. Analysis of the data indicated that commercial bread samples which indicated the use of azodicarbonamide as a flour improver showed statistically significant increases in ethyl carbamate concentrations. The mean increase for treated bread over untreated bread was 66%. When these breads were toasted, the mean increase for treated toast over untreated toast was 56%.

http://www.ncbi.nlm.nih.gov/pubmed/9059589

“Toasting, which was previously shown to increase ethyl carbamate levels, caused even larger increases when Azodicarbonamide or urea had been added.”

Food Additives And Contaminants • January 1997

Ethyl carbamate levels resulting from azodicarbonamide use in bread

Author information

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Abstract

Azodicarbonamide (ADA), a dough conditioner, is an additive approved in the US up to a maximum of 45 mg/kg in flour. The addition of 45 mg/kg of ADA was investigated and found to increase the ethyl carbamate (EC) content of commercially prepared breads by 1-3 micrograms/kg. A similar increase in EC was observed in breads baked in the laboratory with a bread machine. The increase in EC levels appears to depend on a variety of factors, most notably the concentration of ADA added and the time of fermentation. The addition of 20 mg/kg ADA caused only a slight increase, if any, in commercial products but a 2.3 micrograms/kg increase of EC in breads baked with a bread machine. When 100 mg/kg of ascorbic acid was added along with ADA, smaller EC increases were observed. Addition of urea was also found to enhance the EC content of the bread. Toasting, which was previously shown to increase EC levels, caused even larger increases when ADA or urea had been added.

http://www.ncbi.nlm.nih.gov/pubmed/9059587

Nature Medicine • March 1997

Azodicarbonamide inhibits HIV-1 replication by targeting the nucleocapsid protein

Author information

Frederick National Laboratory
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Rice WG1, Turpin JA, Huang M, Clanton D, Buckheit RW Jr, Covell DG, Wallqvist A, McDonnell NB, DeGuzman RN, Summers MF, Zalkow L, Bader JP, Haugwitz RD, Sausville EA.

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Abstract

Nucleocapsid p7 (NCp7) proteins of human immunodeficiency virus type 1 (HIV-1) contain two zinc binding domains of the sequence Cys-(X)2-Cys-(X)4-His-(X)4-Cys (CCHC). The spacing pattern and metal-chelating residues (3 Cys, 1 His) of these nucleocapside CCHC zinc fingers are highly conserved among retroviruses. These CCHC domains are required during both the early and late phases of retroviral replication, making them attractive targets for antiviral agents. toward that end, we have identified a number of antiviral chemotypes that electrophilically attack the sulfur atoms of the zinc-coordinating cysteine residues of the domains. Such nucleocapside inhibitors were directly virucidal by preventing the initiation of reverse transcription and blocked formation of infectious virus from cells through modification of CCHC domains within Gag precursors. Herein we report that azodicarbonamide (ADA) represents a new compound that inhibits HIV-1 and a broad range of retroviruses by targeting the the nucleocapsid CCHC domains. Vandevelde et al. also recently disclosed that ADA inhibits HIV-1 infection via an unidentified mechanism and that ADA was introduced into Phase I/II clinical trials in Europe for advanced AIDS. These studies distinguish ADA as the first known nucleocapsid inhibitor to progress to human trials and provide a lead compound for drug optimization.

http://www.ncbi.nlm.nih.gov/pubmed/9055865

British Journal Of Industrial Medicine • January 1989

Occupational asthma after exposure to azodicarbonamide: report of four cases

Normand JC1, Grange F, Hernandez C,
Ganay A, Davezies P, Bergeret A, Prost G.

Author information

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Abstract

Azodicarbonamide (Chemical Abstract Service Registry No 123.77.3) is an organic low molecular weight agent used for blowing and foaming plastics. Finely ground azodicarbonamide can be a pulmonary and sometimes a cutaneous acute sensitiser. Four cases of work related asthma are reported.

Full text, graph and 13 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1009725/?page=3

Xenobiotica • September 1989

Azodicarbonamide: methods for the analysis in tissues of rats and inhalation disposition

Author information

Bechtold WE1, Medinsky MA, Cheng YS, Hobbs CH.

Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM 87185

Abstract

1. A method has been developed for measuring azodicarbonamide (ADA) and its metabolite biurea in tissues of rat. The method is based on the reaction of ADA with triphenylphosphine; the derivative so formed was isolated and quantified using reversed-phase h.p.l.c. Quantification was by u.v. detection with 14C-ADA as internal standard. Biurea was measured by oxidation to ADA, followed by treatment as described above.

2. When biurea was added to tissues at 100-400 micrograms, recoveries of 92-125% were observed. In contrast, recoveries of ADA added to tissues were generally much less than 100% and could not be reliably determined. The inability to quantify ADA added to tissues was ascribed to its rapid and facile reduction by tissue sulphydryl groups.

3. When rats were exposed to ADA aerosol concentrations of 200, 100, 50 and 0 mg/m3 for 13 weeks by inhalation, a non-linear dose-dependent accumulation of biurea was observed in lungs. No ADA was detected in lungs. Neither biurea nor ADA could be detected in kidneys.

http://www.ncbi.nlm.nih.gov/pubmed/2815834

AZODICARBONAMIDE
IT DOES A BODY GOOD

Contact Dermatitis • August 1988

Contact Dermatitis from azodicarbonamide in earplugs

Author information

Yates VM1, Dixon JE.

Royal Infirmary, Blackburn, UK

This Report Available By Purchase Only

http://www.ncbi.nlm.nih.gov/pubmed/2972529

American Industrial Hygiene Association Journal • May 1987

Development and use of a sampling and analytical method for azodicarbonamide

By S.H. Ahrenholz and C.E. Neumeister

Abstract

Azodicarbonamide is a medium temperature blowing agent used in the production of foamed polymers. Because of worker concern over health effects associated with its use, researchers from the National Institute for Occupational Safety and Health (NIOSH) conducted two health hazard evaluations. This paper describes the health concerns, the sampling and analytical method used, the environments sampled and the results of these surveys. Environmental samples were collected on Teflon filters for total dust and airborne concentration of azodicarbonamide. Analysis was accomplished by high performance liquid chromatography with identification and quantitation by UV detector response ratioing. Use of this method provided the sensitivity and specificity to analyze airborne azodicarbonamide concentrations and allowed evaluation of a workplace environment for a respiratory health hazard.

http://www.ncbi.nlm.nih.gov/pubmed/3591665

“These results suggest respiratory symptom causation by some combination of azodicarbonamide itself, reaction products of azodicarbonamide formed during injection molding, or other unidentified agents uniquely associated with the process of injection molding with azodicarbonamide foaming agent.”

American Journal Of Industrial Medicine • December 1987

Respiratory symptoms associated with the use of azodicarbonamide foaming agent in a plastics injection molding facility

Whitehead LW, Robins TG, Fine LJ, Hansen DJ.

Abstract

Respiratory health variables were studied cross-sectionally in 227 employees of a plastics molding facility where numerous complaints had been apparently associated with the use of azodicarbonamide foaming agent in injection molding. Pre- and postshift respiratory status measures and azodicarbonamide concentrations were also obtained for 17 employees. Cross-sectional pulmonary function differences by injection molding status were not observed. Modest decrements in pulmonary function measures were observed between start and end of shift but with no dose-effect relationship. A strong association was observed for injection molding workers for eye/nose/throat irritation, cough, and wheezing. Additionally, wheezing, chest tightness, and symptoms of chronic bronchitis were strongly associated with work in injection molding during periods in which azodicarbonamide was in use. These results suggest respiratory symptom causation by some combination of azodicarbonamide itself, reaction products of azodicarbonamide formed during injection molding, or other unidentified agents uniquely associated with the process of injection molding with azodicarbonamide foaming agent.

http://www.ncbi.nlm.nih.gov/pubmed/3812500

Progress In Clinical And Biological Research • October 1984

Toxicity of the components of poly(vinylchloride) polymers additives

By L. Fishbein

Abstract

“The salient features of the toxicity of a number of additives used in polyvinyl chloride polymers were reviewed with primary emphasis on the toxicity of plasticizers (e.g., diethylhexyl phthalate and its metabolites, butylbenzylphthalate and di(2-ethylhexyl)adipate), heat stabilizers (e.g., organotin and lead stabilizers), blowing agents (e.g., **azodicarbonamide**), free-radical initiators (e.g., benzoylperoxide, lauroyl peroxide, tert-butylhydroperoxide and di-tert.butylperoxide, and flame retardants (e.g., decabromodiphenyl oxide). **The paucity of toxicity data on the vast majority of PVC additives should be stressed.**”

http://www.ncbi.nlm.nih.gov/pubmed/6371824

Wonder what’s in the bread?

Thorax • December 1981

Occupational asthma caused by a plastics blowing agent, azodicarbonamide

By A.J. Slovak

Abstract

“A prevalence study of occupational asthma was carried out by questionnaire in 1980 among a group of 151 workers who had been exposed to azodicarbonamide dust in the process of its manufacture. Twenty-eight (18.5%) people without previous asthma gave a history of episodes of late onset asthma after exposure to azodicarbonamide. Re-exposure caused repetition and worsening of symptoms. Immediate removal from further exposure resulted in rapid cessation of symptoms without further recurrence. Seven of 13 sensitised individuals who were still exposed three months after the onset of disease developed prolonged airways hyperreactivity to common environmental irritants. Azodicarbonamide should be excluded as a causative agent in plastics and rubber industry workers complaining of occupational asthma.”

Full text PDF

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC471857/pdf/thorax00192-0026.pdf

The Journal Of Occupational Medicine • June 1977

Apparent effect of an azodicarbonamide on the lungs
A preliminary report

Ferris BG Jr, Peters JM, Burgess WA, Cherry RB.

Abstract

"This preliminary study calls attention to the possible pulmonary reactivity of inhaled finely ground azodicarbonamide to which small numbers of workers may be exposed. The conditions in this particular plant involving significant exposure to respirable dust in the mg/m3 range may occur in other plants handling these fine powders. Engineering controls are indicated to protect the workers. We hope that this report will stimulate more detailed studies to validate or refute these observations."

http://www.ncbi.nlm.nih.gov/pubmed/874590

Coca Cola, Pepsi Cola & Carbonated Drinks

The Peer Review

Too Much Soda Might Actually Kill You

Soda and sugary drinks may lead to an estimated 184,000 deaths among adults every year, according to a recent study by researchers at Tufts University published in the American Heart Association journal Circulation. The study analyzed consumption patterns from 62 dietary surveys including 611,971 individuals between 1980 and 2010 across 51 countries, along with data on national availability of sugar in 187 countries and other information. Sugar-sweetened beverages consumption may have been responsible for approximately 133,000 deaths from diabetes 45,000 deaths from cardiovascular disease and 6,450 deaths from cancer, the study found. To be fair, The American Beverage Association published a lengthy rebuttal: "This study does not show that consuming sugar-sweetened beverages causes chronic diseases and the authors themselves acknowledge that they are at best estimating effects of sugar-sweetened beverage consumption."

Rising consumption of sugary drinks has also been a major contributor to the obesity epidemic, according to a 2012 report published by the Institute of Medicine. Some 28% of American adults defined themselves as obese in 2014, according to the Well-Being Index calculated by market research group Gallup and health-care consultancy Healthways. And too much sugar consumption is one of the most direct causes of Type 2 diabetes, says Margo G. Wootan, director of nutrition policy at the Washington, D.C.-based nonprofit Center for Science in the Public Interest. In fact, drinking one to two sugary drinks per day increases the risk of Type 2 diabetes by 26%, a 2010 study published by the Diabetes Journal found.

People aren't losing their thirst, but they are going back to basics. Water is one of the fastest-growing segments of the beverage industry, studies suggest, while sales for traditional fizzy drinks are on the decline. Soda consumption in the U.S. fell 1% to 12.76 billion gallons in 2014, the 10th consecutive year of decline, according to industry tracker Beverage Marketing Corp., making 2014 the lowest per-capita consumption of soft drinks since in nearly three decades. Consumers are choosing more low- and no-calorie beverages, says a spokesman for the American Beverage Association.

The decline is part of a shift in consumer tastes. In the four decades since the launch of Perrier water in the U.S. market in the mid-1970s, American consumption of bottled water has surged 2,700%, from 354 million gallons in 1976 to 9.7 billion gallons in 2012, according to Nick Colas, chief market strategist at ConvergEx, a brokerage and a services firm. Last year, around 11 billion gallons of bottled water was consumed in the U.S., up more than 7% on the previous year, according to the industry research group, Beverage Marketing Corporation. That said, many soda makers now also own bottled-water brands. Coca-Cola owns Dasani, PepsiCo owns Aquafina, and Dr Pepper Snapple owns Deja Blue.

While fizzy-drink sales may have lost their fizz, soda isn't going away any time soon. A decade ago, 80% of Americans consumed at least one such beverage every two weeks, says Harry Balzer, chief industry analyst for market research firm NPD Group. Today, 72% continue to do so. "Soda is still a very popular part of the American diet," he says. "More Americans drink soda than drink energy drinks and coffee."

Diet soda may not be good for you either. Overweight and obese adults drink more diet beverages than healthy-weight adults — yet still consume significantly more food calories than overweight and obese adults who drink sugar-sweetened beverages, a study published in the January 2014 American Journal of Public Health found. It looked at cross-sectional data of nearly 24,000 Americans over a 10-year period, says co-author Sara Bleich, associate professor of health policy at the Johns Hopkins Bloomberg School of Public Health in Baltimore "The folks that drink diet sodas consume a lot more calories," she says.

Another 2013 study by French researchers published in The American Journal of Clinical Nutrition found a strong correlation between diet drinks and increased risk of Type 2 diabetes. Women who drink "light" beverages tend to consume 43% more than women who drink normal sugary drinks — the study found. Furthermore, when consumed in equal quantities, artificially sweetened drinks were associated with an increased risk of developing diabetes.

When efforts by public-health advocates and senate leaders to consider new federal taxes on soda and other sugary drinks escalate, experts say, so does the lobbying spending of soda companies. Between 2005 and 2009, as public-health advocates were making a big push to tax soda at the national level, lobbying spending by the soda industry rose more than 30-fold, to $40.3 million in 2009.That spending effort contributed to the defeat of the proposals at the national level.

The bottom line, as you'll see based on the peer review on sodas and sugary drinks, is that these sugary drinks, regardless of what they're sweetened with, negatively effect human health and regular use can cause cancer, diabetes and more. It's best to avoid them completely and spend your money on products with nutritional value.

“Low-income countries need to be wary of these practices and institute controls on advertising to ensure that powerful multinational companies cannot exploit emerging markets at the expense of public health. We call on leaders of the public and private sectors in Uganda and elsewhere to guard against such dangerous conflicts of interest.”

The Lancet • January 2016

Coca-Cola’s multifaceted threat to global public health

By Andrew Flynn and Sam Agatre Okuonzi

The Lancet Editorial (Oct 3, p 1312) correctly identified that Coca-Cola’s goals differ greatly from those of the public health and research institutions that it funds.1 All organisations concerned with public interest need to guard against conflict of interest from Coca-Cola’s vast marketing campaigns to safeguard public health. One such marketing campaign involves advertisements at public schools in Uganda (figure), which illustrates Coca-Cola’s predatory use of corporate funding, in the name of “corporate social responsibility”, to target children in a setting of inadequate public funding for education.

Exposure to advertising of sugar-sweetened beverages leads to increased consumption that in turn raises the risk of obesity, diabetes, cardiovascular disease, liver disease, and other health problems.2, 3, 4 By displaying advertisements on school signs, manufacturers like Coca-Cola prey on vulnerable youth and contribute to the global epidemic of non-communicable diseases. In Uganda and other low-income countries, diabetes prevalence is quickly growing, as is the consumption of sugar-sweetened beverages.5, 6 As the industry increasingly relies on emerging markets such as Uganda’s, we expect this disturbing trend to continue unless preventive action is taken.

Low-income countries need to be wary of these practices and institute controls on advertising to ensure that powerful multinational companies cannot exploit emerging markets at the expense of public health. Evidence-based policy interventions that limit marketing of sugar-sweetened beverages, especially to children, can reduce consumption of these harmful products.4 We call on leaders of the public and private sectors in Uganda and elsewhere to guard against such dangerous conflicts of interest. We declare no competing interests.

A Coca-Cola advertisement on the sign outside a public primary school in northern Uganda

Full text, PDF

http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)01290-8.pdf

“The results of this study demonstrated that carbonated soft drinks induced oxidative stress and altered the expression of certain genes that are associated with the brain activity and thus should be consumed with caution.”

Molecular Medicine Reports • February 2016

Carbonated soft drinks induce oxidative stress and alter the expression of certain genes in the brains of Wistar rats

Author information

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Abstract

In Saudi Arabia, the consumption of carbonated soft drinks is common and often occurs with each meal. Carbonated soft drink consumption has been shown to exhibit effects on the liver, kidney and bone. However, the effects of these soft drinks on brain activity have not been widely examined, particularly at the gene level. Therefore, the current study was conducted with the aim of evaluating the effects of chronic carbonated soft drink consumption on oxidative stress, brain gene biomarkers associated with aggression and brain histology. In total, 40 male Wistar rats were divided into four groups: Group 1 served as a control and was provided access to food and water ad libitum; and groups 2-4 were given free access to food and carbonated soft drinks only (Cola for group 2, Pepsi for group 3 and 7-UP for group 4). Animals were maintained on these diets for 3 consecutive months. Upon completion of the experimental period, animals were sacrificed and serological and histopathological analyses were performed on blood and tissues samples. Reverse transcription-polymerase chain reaction was used to analyze alterations in gene expression levels. Results revealed that carbonated soft drinks increased the serum levels of malondialdehyde (MDA). Carbonated soft drinks were also observed to downregulate the expression of antioxidants glutathione reductase (GR), catalase and glutathione peroxidase (GPx) in the brain when compared with that in the control rats. Rats administered carbonated soft drinks also exhibited decreased monoamine oxidase A (MAO-A) and acetylcholine esterase (AChE) serum and mRNA levels in the brain. In addition, soft drink consumption upregulated mRNA expression of dopamine D2 receptor (DD2R), while 5-hydroxytryptamine transporter (5-HTT) expression was decreased. However, following histological examination, all rats had a normal brain structure. The results of this study demonstrated that carbonated soft drinks induced oxidative stress and altered the expression of certain genes that are associated with the brain activity and thus should be consumed with caution.

http://www.ncbi.nlm.nih.gov/pubmed/26936207

“The results of this study demonstrated that that carbonated soft drinks induced oxidative stress and altered the expression of certain genes that are associated with the brain activity and thus should be consumed with caution.”

Molecular Medicine Reports • April 2016

Carbonated soft drinks induce oxidative stress and alter the expression of certain genes in the brains of Wistar rats

Author information

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Abstract

In Saudi Arabia, the consumption of carbonated soft drinks is common and often occurs with each meal. Carbonated soft drink consumption has been shown to exhibit effects on the liver, kidney and bone. However, the effects of these soft drinks on brain activity have not been widely examined, particularly at the gene level. Therefore, the current study was conducted with the aim of evaluating the effects of chronic carbonated soft drink consumption on oxidative stress, brain gene biomarkers associated with aggression and brain histology. In total, 40 male Wistar rats were divided into four groups: Group 1 served as a control and was provided access to food and water ad libitum; and groups 2-4 were given free access to food and carbonated soft drinks only (Cola for group 2, Pepsi for group 3 and 7-UP for group 4). Animals were maintained on these diets for 3 consecutive months. Upon completion of the experimental period, animals were sacrificed and serological and histopathological analyses were performed on blood and tissues samples. Reverse transcription-polymerase chain reaction was used to analyze alterations in gene expression levels. Results revealed that carbonated soft drinks increased the serum levels of malondialdehyde (MDA). Carbonated soft drinks were also observed to downregulate the expression of antioxidants glutathione reductase (GR), catalase and glutathione peroxidase (GPx) in the brain when compared with that in the control rats. Rats administered carbonated soft drinks also exhibited decreased monoamine oxidase A (MAO-A) and acetylcholine esterase (AChE) serum and mRNA levels in the brain. In addition, soft drink consumption upregulated mRNA expression of dopamine D2 receptor (DD2R), while 5-hydroxytryptamine transporter (5-HTT) expression was decreased. However, following histological examination, all rats had a normal brain structure. The results of this study demonstrated that that carbonated soft drinks induced oxidative stress and altered the expression of certain genes that are associated with the brain activity and thus should be consumed with caution.

http://www.ncbi.nlm.nih.gov/pubmed/26936207

BRAND COMPETITION
And The Food We Eat

According to the peer review, most basic carbonated soft drinks induce oxidative stress, metabolic disorders in later life, the caramel coloring exposes us to 4-methylimidazole, a confirmed cancer causing chemical, soft drinks are errosive and regular use causes enamel loss and severe tooth decay and in long-term bioassays carbonated soft drinks cause a statistically significant increase in malignant mammary tumors in females. That should be enough to avoid these drinks completely but few people have that information. Without it you're lost among a minefield of false advertising and outright lies. The methodology behind marketing these products successfully is designed around public deception and advertising campaigns that appeal to your deepest child-like emotions. If people actually understood the health issues that these various drinks are responsible for, especially with regular use, they wouldn't drink them at all. Public deception is a necessary component of growth and profitability when you sell poison.

Coca-Cola VS pepsi

You Can Choose Your Poison From The Many 100s Of Products Marketed By These Two Companies

“Deleterious histopathological changes were reported predominantly in the bone and liver of the Coca-Cola and Pepsi groups. In conclusion, a very strict caution must be considered with soft drink consumption due to the increase in oxidative stress biomarkers and disruption in the expression of certain genes associated with the bio-vital function of both the liver and kidney.”

Molecular Medicine Reports • June 2016

Chronic effects of soft drink consumption on the health state of Wistar rats: A biochemical, genetic and histopathological study

Author information

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Abstract

The present study was performed to examine the effects of chronic soft drink consumption (SDC) on oxidative stress, biochemical alterations, gene biomarkers and histopathology of bone, liver and kidney. Free drinking water of adult male Wistar rats was substituted with three different soft drinks: Coca-Cola, Pepsi and 7-Up, for three consecutive months. The serum and organs were collected for examining the biochemical parameters associated with bone, liver and kidney functions. Semi-quantitative reverse transcription polymerase chain reaction was used to observe the changes in the expression of genes in the liver and kidney, which are associated with oxidative stress resistance. Histopathological investigations were performed to determine the changes in bone, liver and kidney tissues using hematoxylin and eosin stains. SDC affected liver, kidney and bone function biomarkers. Soft drinks increased oxidative stress, which is represented by an increase in malondialdehyde and a decrease in antioxidant levels. SDC affected serum mineral levels, particularly calcium and phosphorus. Soft drinks downregulated the expression levels of glutathione-S-transferase and super oxide dismutase in the liver compared with that of control rats. Rats administered Coca-Cola exhibited a hepatic decrease in the mRNA expression of ß2-macroglobulin compared with rats administered Pepsi and 7-Up. On the other hand, SDC increased the mRNA expression of ß1-acid glycoprotein. The present renal studies revealed that Coca-Cola increased the mRNA expression levels of desmin, angiotensinogen and angiotensinogen receptor compared with the other groups, together with mild congestion in renal histopathology. Deleterious histopathological changes were reported predominantly in the bone and liver of the Coca-Cola and Pepsi groups. In conclusion, a very strict caution must be considered with SDC due to the increase in oxidative stress biomarkers and disruption in the expression of certain genes associated with the bio-vital function of both the liver and kidney.

Full text, photos, graphs, charts and 49 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4878564/

“Our results suggest that combined effect of prenatal Maillard reaction products load and postnatal Coca-Cola drinking may play a role in development of metabolic disorders in later life.”

Croation Medical Journal • January 2015

Prenatal dietary load of Maillard reaction products combined with postnatal Coca-Cola drinking affects metabolic status of female Wistar rats

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Abstract

Aim

To assess the impact of prenatal exposure to Maillard reaction products (MRPs) -rich diet and postnatal Coca-Cola consumption on metabolic status of female rats. Diet rich in MRPs and consumption of saccharose/fructose sweetened soft drinks is presumed to impose increased risk of development of cardiometabolic afflictions, such as obesity or insulin resistance.

Methods

At the first day of pregnancy, 9 female Wistar rats were randomized into two groups, pair-fed either with standard rat chow (MRP-) or MRPs-rich diet (MRP+). Offspring from each group of mothers was divided into two groups and given either water (Cola-) or Coca-Cola (Cola+) for drinking ad libitum for 18 days. Oral glucose tolerance test was performed, and circulating markers of inflammation, oxidative stress, glucose and lipid metabolism were assessed.

Results

MRP+ groups had higher weight gain, significantly so in the MRP+/Cola- vs MRP-/Cola-. Both prenatal and postnatal intervention increased carboxymethyllysine levels and semicarbazide-sensitive amine oxidase activity, both significantly higher in MRP+/Cola+ than in MRP-/Cola-. Total antioxidant capacity was lower in MRP+ groups, with significant decrease in MRP+/Cola+ vs MRP-/Cola+. Rats drinking Coca-Cola had higher insulin, homeostatic model assessment of insulin resistance, heart rate, advanced oxidation of protein products, triacylglycerols, and oxidative stress markers measured as thiobarbituric acid reactive substances compared to rats drinking water, with no visible effect of MRPs-rich diet.

Conclusion

Metabolic status of rats was affected both by prenatal and postnatal dietary intervention. Our results suggest that combined effect of prenatal MRPs load and postnatal Coca-Cola drinking may play a role in development of metabolic disorders in later life.

Full text, graphs, charts and 59 references

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4410178/pdf/CroatMedJ_56_0094.pdf

The MAILLARD REACTION & Advanced Glycation Endproducts (AGEs)

The Maillard reaction is a chemical reaction between amino acids and reducing sugars that gives browned food its desirable flavor. Seared steaks, pan-fried dumplings, cookies (widely known in the United Kingdom as biscuits), breads, toasted marshmallows, and many other foods undergo this reaction. It is named after French chemist Louis-Camille Maillard, who first described it in 1912 while attempting to reproduce biological protein synthesis.

The reaction is a form of non-enzymatic browning which typically proceeds rapidly from around 140 to 165 °C (284 to 329 °F). At higher temperatures, caramelization and subsequently pyrolysis become more pronounced.

The reactive carbonyl group of the sugar reacts with the nucleophilic amino group of the amino acid, and forms a complex mixture of poorly characterized molecules responsible for a range of odors and flavors. This process is accelerated in an alkaline environment—for example, lye applied to darken pretzels—as the amino groups (RNH3+) are deprotonated and, hence, have an increased nucleophilicity. The type of the amino acid determines the resulting flavor. This reaction is the basis of the flavoring industry. At high temperatures, a potential carcinogen called acrylamide can be formed.

In the process, hundreds of different flavor compounds are created. These compounds, in turn, break down to form yet more new flavor compounds, and so on. Each type of food has a very distinctive set of flavor compounds that are formed during the Maillard reaction. It is these same compounds that flavor scientists have used over the years to make reaction flavors.

In 1913 Maillard published a paper to explain what happens when amino acids react with sugars at elevated temperatures. However, it was chemist John E. Hodge, working at the U.S. Department of Agriculture in Peoria, Illinois, who published a paper in 1953 that established a mechanism for the Maillard reaction.

The Maillard reaction is responsible for many colors and flavors in foods:

- The browning of various meats like steak, when seared and grilled.
- The browning and umami taste in fried onions.
- Toast.
- The darkened crust of baked goods like pretzels and bread.
- The golden-brown color of French fries.
- Malted barley, found in malt whiskey or beer.
- Dried or condensed milk.
- Roasted coffee.
- Dulce de leche.
- Black garlic.

Six-Acetyl-2,3,4,5-tetrahydropyridine is responsible for the biscuit or cracker-like flavor present in baked goods like bread, popcorn, and tortilla products. The structurally related compound 2-acetyl-1-pyrroline has a similar smell, and occurs also naturally without heating and gives varieties of cooked rice and the herb pandan (Pandanus amaryllifolius) their typical smells. Both compounds have odor thresholds below 0.06 ng/l.

The browning reactions that occur when meat is roasted or seared are complicated, and occur mostly by Maillard browning with contributions from other chemical reactions, including the breakdown of the tetrapyrrole rings of the muscle protein myoglobin.

Caramelization is an entirely different process from Maillard browning, though the results of the two processes are sometimes similar to the naked eye (and tastebuds). Caramelization may sometimes cause browning in the same foods in which the Maillard reaction occurs, but the two processes are distinct. They both are promoted by heating, but the Maillard reaction involves amino acids, as discussed above, whereas caramelization is simply the pyrolysis of certain sugars. The following things are a result of the Maillard browning reaction:

- Caramel made from milk and sugar, especially in candies: Milk is high in protein (amino acids), and browning of food involving this complex ingredient would most likely include Maillard reactions.
- Chocolate
- Lightly roasted peanuts

In making silage, excess heat causes the Maillard reaction to occur, which reduces the amount of energy and protein available to the animals who feed on it. A pressure cooker is well suited for achieving the higher temperatures often required for the Maillard reaction to occur (depending upon what is being prepared).

The Maillard reaction also occurs in the human body. It is a step in the formation of advanced glycation endproducts (AGEs). It is tracked by measuring pentosidine. Although the Maillard reaction has been studied most extensively in foods, it has also shown a correlation in numerous different diseases in the human body, in particular degenerative eye diseases. In general, these diseases are due to the accumulation of AGEs on nucleic acids, proteins, and lipids. Though AGEs have numerous origins, they can form from the oxidation and dehydration of Amadori adducts, which themselves are products of nonenzymatic Maillard reactions. Apart from ocular diseases, whose correlation with Maillard chemistry has been more recently studied, the formation of AGEs has also proven to contribute to a wide range of human diseases that include diabetic complications, pulmonary fibrosis, and neurodegeneration.

PLoS One • February 2015

Caramel color in soft drinks and exposure to 4-methylimidazole: a quantitative risk assessment

Author information

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Abstract

Caramel color is added to many widely-consumed beverages as a colorant. Consumers of these beverages can be exposed to 4-methylimidazole (4-MEI), a potential carcinogen formed during its manufacture. California's Proposition 65 law requires that beverages containing 4-MEI concentrations corresponding to exposures that pose excess cancer risks > 1 case per 100,000 exposed persons (29 µg 4-MEI/day) carry warning labels. Using ultrahigh-performance liquid chromatography-tandem mass spectrometry, we assessed 4-MEI concentrations in 12 beverages purchased in California and a geographically distant metropolitan area (New York) in which warning labels are not required. In addition, we characterized beverage consumption by age and race/ethnicity (using weighted means calculated from logistic regressions) and assessed 4-MEI exposure and resulting cancer risks and US population cancer burdens attributable to beverage consumption. Data on beverage consumption were obtained from the National Health and Nutrition Examination Survey, dose-response data for 4-MEI were obtained from the California Environmental Protection Agency Office of Environmental Health Hazards Assessment, and data on population characteristics were obtained from the U.S. Census Bureau. Of the 12 beverages, Malta Goya had the highest 4-MEI concentration (915.8 to 963.3µg/L), lifetime average daily dose (LADD - 8.04x10-3 mg/kgBW-day), lifetime excess cancer risk (1.93x10-4) and burden (5,011 cancer cases in the U.S. population over 70 years); Coca-Cola had the lowest value of each (4-MEI: 9.5 to 11.7µg/L; LADD: 1.01x10-4 mg/kgBW-day; risk: 1.92x10-6; and burden: 76 cases). 4-MEI concentrations varied considerably by soda and state/area of purchase, but were generally consistent across lots of the same beverage purchased in the same state/area. Routine consumption of certain beverages can result in 4-MEI exposures > 29 µg/day. State regulatory standards appear to have been effective in reducing exposure to carcinogens in some beverages. Federal regulation of 4-MEI in caramel color may be appropriate.

Full text, graphs, charts, with 26 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4333292/

“... the analysis [of] canned soft drinks and the analytes were found in five of the 10 samples analysed.”

Food Additive Contaminants • Part A • Risk Assessment • February 2015

Determination of synthetic phenolic antioxidants in soft drinks by stir-bar sorptive extraction coupled to gas chromatography-mass spectrometry

Author information

Cacho JI1, Campillo N, Viñas P, Hernández-Córdoba M.

Abstract

The synthetic phenolic antioxidants butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and tert-butyl hydroquinone (TBHQ) were pre-concentrated by stir-bar sorptive extraction and thermally desorbed (SBSE-TD) before analysis by GC-MS. Several parameters affecting the derivatisation step and both SBSE extraction and thermal desorption were carefully optimised. When the analyses of BHA and TBHQ in their acetylated, silylated and underivatised forms were compared, the best results were obtained when the in-situ derivatisation procedure with acetic anhydride was employed. Quantification was carried out using carvacrol as the internal standard, providing quantification limits of between 0.11 and 0.15 ng ml(-1), depending on the compound. Recovery assays for samples spiked at two concentration levels, 1 and 5 ng ml(-1), provided recoveries in the 81-117% range. The proposed method was applied in the analysis canned soft drinks and the analytes were found in five of the 10 samples analysed.

http://www.ncbi.nlm.nih.gov/pubmed/25622305

“This report presents the first case of a gastric bezoar successfully treated by endoscopic fragmentation in combination with Pepsi-Cola® administration ...”

The American Journal Of Case Reports • July 2015

Gastric Bezoar Treatment by Endoscopic Fragmentation in Combination with Pepsi-Cola® Administration

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Abstract

BACKGROUND

Although bezoar dissolution by Coca-Cola® has been described in case reports and case series, to the best of our knowledge, the usefulness of other cola products such as Pepsi-Cola® has never been reported in the English literature.

CASE REPORT

An 86-year-old Taiwanese man was diagnosed with a gastric bezoar. Endoscopic fragmentation with a polypectomy snare was attempted twice but failed to remove the bezoar. Subsequently, 500 mL of Pepsi NEX Zero® was administered daily for 4 days via nasogastric tube. The bezoar was softened and successfully fragmented by the polypectomy snare and needle-knife devices on the third attempt.

CONCLUSIONS

This report presents the first case of a gastric bezoar successfully treated by endoscopic fragmentation in combination with Pepsi-Cola® administration, suggesting the possible utility of cola beverages in bezoar treatment, regardless of product brands.

Full text, photos and 15 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504408/

Public Health Nutrition • November 2015

Trends in food and beverage television brand appearances viewed by children and adolescents from 2009 to 2014 in the USA

Author information

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Abstract

OBJECTIVE

Public health experts raise concerns about marketing unhealthy products to young people through television (TV) product placements. Coca-Cola brand appearances (product placements) reached a substantial child and adolescent audience in 2008, but additional brands now sponsor popular programming. We aimed to quantify child and adolescent exposure to food and beverage appearances since 2008.

DESIGN

In 2015, we purchased Nielsen data on occurrences and child/adolescent exposure to food, beverage and restaurant brand appearances on US prime-time TV from 2009 to 2014, and analysed appearances by product category, company, brand and year. We compared exposure to appearances with exposure to traditional commercials for top brands.

SETTING

Nationally representative panel of approximately 20 000 TV-viewing households.

SUBJECTS:

Children (2-11 years) and adolescents (12-17 years).

RESULTS

Exposure to food and beverage brand appearances peaked in 2012 and declined through 2014. Whereas full-calorie soda brands dominated before 2012, other sugary drink and quick-serve restaurant brands contributed over one-third of appearances viewed by children in 2013 and 2014. Nine hundred and fifty-four companies had brand appearances from 2009 to 2014, but just four were responsible for over half of exposures: The Coca-Cola Company, Dr Pepper Snapple Group, PepsiCo and Starbucks. Approximately half were viewed on reality TV programmes and one sitcom. Each year from 2009 to 2013, brand appearance exposure exceeded traditional advertising exposure for at least one brand.

CONCLUSIONS

Despite recent reductions in brand appearances viewed by young people, some unhealthy branded products continue to be marketed via this method. We suggest policy options to reduce child and adolescent exposure to such appearances.

http://www.ncbi.nlm.nih.gov/pubmed/26586004

British Medical Journal • January 2013

Coca-Cola launches antiobesity advertisements

By JH Tanne
Available for purchase only

http://www.ncbi.nlm.nih.gov/pubmed/23344549

British Medical Journal • December 2015

Coca-Cola funded group set up to promote “energy balance” is disbanded

By Z. Kmietowicz
Available for purchase only

http://www.ncbi.nlm.nih.gov/pubmed/26637498

“An unknown factor is responsible for the increase in [cell] proliferation.”

Annals Of Agricultural And Environmental Medicine • April 2014

Non-alcoholic beverages, unknown influence on cell proliferation—an in vitro study

Author information

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Department of Tissue Engineering, Nicolaus Copernicus University, Bydgoszcz, Poland

Abstract

INTRODUCTION AND OBJECTIVE

The aim of the presented study was to check differences between ‘Diet’ and ‘non-Diet’ soft drinks on cell proliferation.

MATERIALS AND METHODS

Coca Cola and Pepsi Cola of different origin and their dietetic versions were examined at concentrations of 2% and 4%. Fructose and glucose as well as medium alone (control) were examined.

RESULTS

Cell number was higher in media supplemented with soft drinks, compared to control. Proliferation depended on the soft drink concentration and its origin, but not on sugar and calorific content.

CONCLUSIONS

An unknown factor is responsible for the increase in proliferation.

http://www.ncbi.nlm.nih.gov/pubmed/24738507

“By using the interactive and social aspects of Facebook to market products, Energy-Dense, Nutrient-Poor (EDNP) food brands capitalize on users’ social networks and magnify the reach and personal relevance of their marketing messages.”

American Journal Of Public Health • December 2014

Digital Junk: Food And Beverage Marketing On FACEBOOK

Author information

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Becky Freeman, Simon Chapman, and Lesley King are with the School of Public Health, University of Sydney, New South Wales, Australia. Bridget Kelly is with the School of Health and Society, University of Wollongong, New South Wales. Louise Baur is with the Discipline of Paediatrics and Child Health, University of Sydney, New South Wales. Kathy Chapman is with Health Strategies, Cancer Council New South Wales, Woolloomooloo, Australia. Tim Gill is with the Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, New South Wales, Australia.

Abstract

OBJECTIVES

We assessed the amount, reach, and nature of energy-dense, nutrient-poor (EDNP) food and beverage marketing on Facebook.

METHODS

We conducted a content analysis of the marketing techniques used by the 27 most popular food and beverage brand Facebook pages in Australia. We coded content across 19 marketing categories; data were collected from the day each page launched (mean=3.65 years of activity per page).

RESULTS

We analyzed 13 international pages and 14 Australian-based brand pages; 4 brands (Subway, Coca-Cola, Slurpee, Maltesers) had both national and international pages. Pages widely used marketing features unique to social media that increase consumer interaction and engagement. Common techniques were competitions based on user-generated content, interactive games, and apps. Four pages included apps that allowed followers to place an order directly through Facebook. Adolescent and young adult Facebook users appeared most receptive to engaging with this content.

CONCLUSIONS

By using the interactive and social aspects of Facebook to market products, EDNP food brands capitalize on users’ social networks and magnify the reach and personal relevance of their marketing messages.

http://www.ncbi.nlm.nih.gov/pubmed/25322294

Alimentary Pharmacology And Therapeutics • January 2013

Systematic review: Coca-Cola can effectively dissolve gastric phytobezoars as a first-line treatment

Author information

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Abstract

BACKGROUND

Gastric phytobezoars represent the most common bezoars in patients with poor gastric motility. A variety of dissolution therapies and endoscopic fragmentation techniques have been evaluated as conservative treatment so as to avoid surgery.

AIM

To investigate the effectiveness of Coca-Cola for gastric phytobezoars dissolution.

METHODS

We performed a systematic search to identify publications on gastric phytobezoars to assess the efficacy of Coca-Cola as a dissolution therapy. Diospyrobezoars, formed after persimmon ingestion, are a distinct type of phytobezoars characterized by their hard consistency. Thus, these two subgroups of bezoars were compared in terms of successful dissolution.

RESULTS

Over a 10-year period (2002-2012), 24 papers including 46 patients have been published. In 91.3% of the cases, phytobezoar resolution with Coca-Cola administration was successful, either as a single treatment (50%) or combined with further endoscopic techniques, whereas only 4 patients underwent surgery. Phytobezoars were more likely to dissolve after initial attempt with Coca-Cola compared with diospyrobezoars (60.6% vs. 23%, P = 0.022).

CONCLUSIONS

Coca-Cola alone is effective in gastric phytobezoar dissolution in half of the cases and, combined with additional endoscopic methods, is successful in more than 90% of them.

Full text, PDF, charts with 45 references

http://onlinelibrary.wiley.com/doi/10.1111/apt.12141/epdf

PLoS One • April 2013

Does taste matter? How anticipation of cola brands influences gustatory processing in the brain

Author information

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Abstract

"Brands surround us everywhere in daily life. Here we investigate the influences of brand cues on gustatory processing of the same beverage. Participants were led to believe that the brand that announced the administration of a Cola mixture provided correct information about the drink to come. We found stronger fMRI signal in right mOFC during weak compared to strong brand cues in a contrast of parametric modulation with subjective liking. When directly comparing the two strong brands cues, more activation in the right amygdala was found for Coca Cola cues compared with Pepsi Cola cues. During the taste phase the same beverage elicited stronger activation in left ventral striatum when it was previously announced by a strong compared with a weak brand. This effect was stronger in participants who drink Cola infrequently and might therefore point to a stronger reliance on brand cues in less experienced consumers. The present results reveal strong effects of brand labels on neural responses signalling reward."

"The present results reveal strong effects of brand labels on neural responses signalling reward."

Full text, graphs, charts, photos and 36 references

http://www.journals.plos.org/plosone/article?id=10.1371/journal.pone.0061569

Obesity Reviews • March 2012

Drinking to our health: can beverage companies cut calories while maintaining profits?

Author information

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Abstract

Carbonated soft drinks and other beverages make up an increasing percentage of energy intake, and there are rising public health concerns about the links between consumption of sugar-sweetened beverages and weight gain, obesity, and other cardiometabolic problems. In response, the food and beverage industry claims to be reformulating products, reducing package or portion sizes and introducing healthier options. Comparative analysis on various changes and their potential effects on public health are needed. We conduct a case study using the two largest and most influential producers of sweetened beverages, The Coca-Cola Company and PepsiCo Inc., who together control 34% of the global soft drink market, examining their product portfolios globally and in three critical markets (the United States, Brazil and China) from 2000 to 2010. On a global basis, total revenues and energy per capita sold increased, yet the average energy density (kJ 100 mL(-1)) sold declined slightly, suggesting a shift to lower-calorie products. In the United States, both total energy per capita and average energy density of beverages sold decreased, while the opposite was true in the developing markets of Brazil and China, with total per capita energy increasing greatly in China and, to a lesser extent, in Brazil.

http://www.ncbi.nlm.nih.gov/pubmed/22070346

“As they did with tobacco, public health advocates need to counter industry corporate social responsibility with strong denormalization campaigns to educate the public and policy makers about the effects of soda corporate social responsibility campaigns and the social ills caused by sugary beverages.”

PLoS Medicine • June 2012

Soda and Tobacco Industry Corporate Social Responsibility Campaigns: How Do They Compare?

Lori Dorfman,1 Andrew Cheyne,1,* Lissy C. Friedman,2 Asiya Wadud,1 and Mark Gottlieb2
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Summary Points

• Because sugary beverages are implicated in the global obesity crisis, major soda manufacturers have recently employed elaborate, expensive, multinational corporate social responsibility (CSR) campaigns.

• These campaigns echo the tobacco industry’s use of corporate social responsibility as a means to focus responsibility on consumers rather than on the corporation, bolster the companies’ and their products’ popularity, and to prevent regulation.

• In response to health concerns about their products, soda companies appear to have launched comprehensive corporate social responsibility initiatives sooner than did tobacco companies.

• Unlike tobacco corporate social responsibility campaigns, soda company corporate social responsibility campaigns explicitly aim to increase sales, including among young people.

• As they did with tobacco, public health advocates need to counter industry corporate social responsibility with strong denormalization campaigns to educate the public and policy-makers about the effects of soda corporate social responsibility campaigns and the social ills caused by sugary beverages.

Full text with 119 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378589/

American Journal Of Preventative Medicine • September 2011

Child and adolescent exposure to food and beverage brand appearances during prime-time television programming

Author information

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Abstract

BACKGROUND

The food industry disproportionately markets to young people through product placements. Children and adolescents may be more susceptible to these disguised persuasive attempts.

PURPOSE

Quantify incidence and youth exposure to food and beverage brand appearances within shows on prime-time TV.

METHODS

Data on the number of food, beverage, and restaurant brand appearances within shows during prime-time programming in 2008 were purchased from Nielsen and analyzed by product category and company in 2010. Exposure to these brand appearances by children, adolescents, and adults were examined and compared with exposure to prime-time TV advertisements for the same categories and companies using additional Nielsen data.

RESULTS

Food, beverage, and restaurant brands appeared a total of 35,000 times within prime-time TV programming examined by Nielsen in 2008. Regular soft drinks, traditional restaurants (i.e., not quickserve), and energy/sports drinks made up 60% of all brand appearances. Young people viewed relatively few of these appearances with one notable exception. Coca-Cola products were seen 198 times by the average child and 269 times by the average adolescent during prime-time shows over the year, accounting for 70% of child exposure and 61% of adolescent exposure to brand appearances. One show, American Idol, accounted for more than 95% of these exposures. Exposure of children to Coca-Cola products through traditional advertisements was much less common.

CONCLUSIONS

Brand appearances for most food industry companies, except for Coca-Cola, are relatively rare during prime-time programming with large youth audiences. Coca-Cola has pledged to refrain from advertising to children, yet the average child views almost four Coke appearances on prime-time TV every week. This analysis reveals a substantial, potential loophole in current food industry self-regulatory pledges to advertise only better-for-you foods to children.

http://www.ncbi.nlm.nih.gov/pubmed/21855743

The Journal Of Zhejiang University • May 2009

Dental erosion and severe tooth decay related to soft drinks: a case report and literature review

Author information

Cheng R1, Yang H, Shao MY, Hu T, Zhou XD.

Department of Operative Dentistry and Endodontics, West China College of Stomatology
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Abstract

“Soft drinks have many potential health problems. The inherent acids and sugars have both acidogenic and cariogenic potential, resulting in dental caries and potential enamel erosion. In this report we present a 25-year-old man complaining with the severe worn-out of the front teeth during the past 3 years. He had a history of drinking cola for more than 7 years and had a poor oral hygiene. Severe decays were present in the incisors and the canines, while less severe lesions were noted on the premolars and the molars. The review is to show the relationship between dental erosion and caries and soft drinks. Some efforts have been taken to reduce the harmful effect of soft drinks.”

Full text, photos and 33 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676420/

Social, Cognitive And Affective Neuroscience • March 2008

Prefrontal cortex damage abolishes brand-cued changes in cola preference

Author information

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Abstract

“Human decision-making is remarkably susceptible to commercial advertising, yet the neurobiological basis of this phenomenon remains largely unexplored. With a series of Coke and Pepsi taste tests we show that patients with damage specifically involving ventromedial prefrontal cortex (VMPC), an area important for emotion, did not demonstrate the normal preference bias when exposed to brand information. Both comparison groups (neurologically normal adults and lesion patients with intact VMPC) preferred Pepsi in a blind taste test, but in subsequent taste tests that featured brand information (‘semi-blind’ taste tests), both comparison groups’ preferences were skewed toward Coke, illustrating the so-called ‘Pepsi paradox’. Like comparison groups, the VMPC patients preferred Pepsi in the blind taste test, but unlike comparison groups, the VMPC patients maintained their Pepsi preference in the semi-blind test. The result that VMPC damage abolishes the ‘Pepsi paradox’ suggests that the VMPC is an important part of the neural substrate for translating commercial images into brand preferences.”

Full text, graphs, charts and 43 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2288573/

“Prolonged exposure to soft drinks can lead to significant enamel loss. Non-cola drinks are more erosive than cola drinks.”

General Dentistry • March 2007

Commercial soft drinks: pH and in vitro dissolution of enamel

Author information

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Department of Growth, Development, and Structure, Southern Illinois University School of Dental Medicine, Alton, USA

Abstract

Most soft drinks are acidic in nature and exposure to these drinks may result in enamel erosion. This study sought to measure the pH of 20 commercial brands of soft drinks, the dissolution of enamel resulting from immersion in these drinks, and the influence of pH on enamel loss. Comparison of the erosive potential of cola versus non-cola drinks as well as regular sugared and diet versions of the same brands was undertaken. The pH was measured immediately after opening the soft drink can. Enamel slices obtained from freshly extracted teeth were immersed in the soft drinks and weighed at baseline and after 6, 24, and 48 hours of immersion. Non-cola drinks had significantly higher pH values than cola drinks but showed higher mean percent weight loss. By contrast, sugared versions of the cola and non-cola drinks showed significantly lower pH values and higher mean percent weight loss than their diet counterparts. The pH value of the soft drink did not have a significant influence on the mean percent weight loss ($r = -0.28$). Prolonged exposure to soft drinks can lead to significant enamel loss. Non-cola drinks are more erosive than cola drinks. Sugared versions of cola and non-cola drinks proved to be more erosive than their diet counterparts. The erosive potential of the soft drinks was not related to their pH value.

http://www.ncbi.nlm.nih.gov/pubmed/17333990

“Flavoured sparkling waters should be considered as potentially erosive, and preventive advice on their consumption should recognize them as potentially acidic drinks rather than water with flavouring.”

International Journal Of Paediatric Dentistry • March 2007

The erosive potential of flavoured sparkling water drinks

Brown CJ1, Smith G, Shaw L, Parry J, Smith AJ.

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Abstract

OBJECTIVE

The potential role of acidic drinks in the aetiology of dental erosion is well recognized. Whilst the wide-scale consumption of bottled waters is unlikely to contribute significantly to erosion, the role of flavoured sparkling water drinks is unclear. The aim of this study was to determine the pH, titratable acidity and in vitro erosive potential of a selection of these drinks drawn from the UK market to identify what dietary advice would be appropriate in relation to their consumption.

METHODS

pH was measured using a pH electrode and titratable acidity recorded by titration with 0.1-m NaOH. Erosive potential was assessed using an in vitro dissolution assay with hydroxyapatite powder and electron microscopic examination of surface enamel of extracted human teeth, following exposure to the flavoured sparkling waters for 30 min.

RESULTS

All of the flavoured waters tested showed appreciable titratable acidity (0.344-0.663 mmol) and low pH (2.74-3.34). In the hydroxyapatite dissolution assay, all of the waters demonstrated erosive potential (89-143%) similar to or greater than that of pure orange juice, an established erosive drink. Exposure of the extracted teeth to the flavoured waters resulted in surface changes consistent with erosive dissolution.

CONCLUSIONS

Flavoured sparkling waters should be considered as potentially erosive, and preventive advice on their consumption should recognize them as potentially acidic drinks rather than water with flavouring.

http://www.ncbi.nlm.nih.gov/pubmed/17263857

Journal Of Food Science • August 2007

Caffeine content of prepackaged national-brand and private-label carbonated beverages

Author information

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Abstract

“Caffeine is a well-known stimulant that is added as an ingredient to various carbonated soft drinks. Due to its stimulatory and other physiological effects, individuals desire to know the exact amount of caffeine consumed from these beverages. This study analyzed the caffeine contents of 56 national-brand and 75 private-label store-brand carbonated beverages using high-performance liquid chromatography. Caffeine contents ranged from 4.9 mg/12 oz (IGA Cola) to 74 mg/12 oz (Vault Zero). Some of the more common national-brand carbonated beverages analyzed in this study with their caffeine contents were Coca-Cola (33.9 mg/12 oz), Diet Coke (46.3 mg/12 oz), Pepsi (38.9 mg/12 oz), Diet Pepsi (36.7 mg/12 oz), Dr Pepper (42.6 mg/12 oz), Diet Dr Pepper (44.1 mg/12 oz), Mountain Dew (54.8 mg/12 oz), and Diet Mountain Dew (55.2 mg/12 oz). The Wal-Mart store-brand beverages with their caffeine contents were Sam’s Cola (12.7 mg/12 oz), Sam’s Diet Cola (13.3 mg/12 oz), Dr Thunder (30.6 mg/12 oz), Diet Dr Thunder (29.9 mg/12 oz), and Mountain Lightning (46.5 mg/12 oz). Beverages from 14 other stores were also analyzed. Most store-brand carbonated beverages were found to contain less caffeine than their national-brand counterparts. The wide range of caffeine contents in carbonated beverages indicates that consumers would benefit from the placement of caffeine values on food labels.”

http://www.ncbi.nlm.nih.gov/pubmed/17995675

“The erosive potential within the first minutes of exposure was determined solely by the pH of the drink, and the erosive potential was ten-fold higher in cola drinks compared with juices.”

Journal Of Dental Research • March 2006

Immediate erosive potential of cola drinks and orange juices

Author information

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Abstract

Little is known about the erosive potential of soft drinks within the first minutes of exposure to teeth, and about the potentially protective role of salivary proteins. We hypothesized that the erosive potential is determined primarily by pH and decreases in the presence of salivary proteins. To investigate this, we first added uncoated hydroxyapatite crystals and, second, salivary-protein-coated hydroxyapatite crystals to 20 commercially available cola drinks and orange juices simultaneously, with pH recordings every 15 sec for 3 min. The amount of apatite lost per liter of soft drink per sec was calculated from titratable acidity values to each pH obtained by crystal addition. The erosive potential within the first minutes of exposure was determined solely by the pH of the drink, and the erosive potential was ten-fold higher in cola drinks compared with juices. However, salivary proteins reduced the erosive potential of cola drinks by up to 50%.

http://www.ncbi.nlm.nih.gov/pubmed/16498068

Annals Of The New York Academy Of Sciences • September 2006

Results of long-term carcinogenicity bioassays on Coca-Cola administered to Sprague-Dawley rats

Author information
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Abstract

Coca-Cola was invented in May 1886 in Atlanta, Georgia by a pharmacist who, by accident or design, mixed carbonated water with the syrup of sugar, phosphoric acid, caffeine, and other natural flavors to create what is known as "the world's favorite soft drink." Coca-Cola is currently sold in more than 200 countries and in early 2000, the company sold its 10 billionth unit case of Coca-Cola branded products. Given the worldwide consumption of Coca-Cola, a project of experimental bioassays to study its long-term effects when administered as substitute for drinking water on male and female Sprague-Dawley rats was planned and executed. The objective of the project was to study whether and how long-term consumption of Coca-Cola affects the basic tumorigram of test animals. The bioassays were performed on rats beginning at different ages, namely: (a) on males and females exposed since embryonic life or from 7 weeks of age; and (b) on males and females exposed from 30, 39, or 55 weeks of age. Overall, the project included 1999 rats. During the biophase, data were collected on fluid and feed consumption, body weight, and survival. Animals were kept under observation until spontaneous death and underwent complete necropsy. The results indicate: (a) an increase in body weight in all treated animals; (b) a statistically significant increase of the incidence in females, both breeders and offspring, bearing malignant mammary tumors; (c) a statistically significant increase in the incidence of exocrine ademonas of the pancreas in both male and female breeders and offspring; and (d) an increased incidence, albeit not statistically significant, of pancreatic islet cell carcinomas in females, a malignant tumor which occurs very rarely in our historical controls. On the basis of the results of this study, excessive consumption of regular soft-drinks should be generally discouraged, in particular for children and adolescents.

http://www.ncbi.nlm.nih.gov/pubmed/17119251

"The results indicate:

(a) an increase in body weight in all treated animals;

(b) a statistically significant increase of the incidence in females, both breeders and offspring, bearing malignant mammary tumors;

(c) a statistically significant increase in the incidence of exocrine ademonas of the pancreas in both male and female breeders and offspring; and

(d) an increased incidence, albeit not statistically significant, of pancreatic islet cell carcinomas in females, a malignant tumor which occurs very rarely in our historical controls.

On the basis of the results of this study, excessive consumption of regular soft-drinks should be generally discouraged, in particular for children and adolescents."

“Thus, the trend towards a replacement of milk with cola and other soft drinks, which results in a low calcium intake, may negatively affect bone health as indicated by this short-term study.”

Osteoporos International • December 2005

Short-term effects on bone turnover of replacing milk with cola beverages: a 10-day interventional study in young men

Author information
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Abstract

In the Western world, increased consumption of carbonated soft drinks combined with a decreasing intake of milk may increase the risk of osteoporosis. This study was designed to reflect the trend of replacing milk with carbonated beverages in a group of young men on a low-calcium diet and studies the effects of this replacement on calcium homeostasis and bone turnover. This controlled crossover intervention study included 11 healthy men (22-29 years) who were given a low-calcium basic diet in two 10-day intervention periods with an intervening 10-day washout. During one period, they drank 2.5 l of Coca Cola per day and during the other period 2.5 l of semi-skimmed milk. Serum concentrations of calcium, phosphate, 25-hydroxycholecalciferol, 1,25-dihydroxycholecalciferol (1,25(OH)2D), osteocalcin, bone-specific alkaline phosphatase (B-ALP) and cross-linked C-telopeptides (CTX), plasma intact parathyroid hormone (PTH) and urinary cross-linked N-telopeptides (NTX) were determined at baseline and endpoint of each intervention period. An increase in serum phosphate ($P<0.001$), 1,25(OH)2D ($P<0.001$), PTH ($P=0.046$) and osteocalcin ($P<0.001$) was observed in the cola period compared to the milk period. Also, bone resorption was significantly increased following the cola period, seen as increased serum CTX ($P<0.001$) and urinary NTX ($P<0.001$) compared to the milk period. No changes were observed in serum concentrations of calcium or B-ALP. This study demonstrates that over a 10-day period high intake of cola with a low-calcium diet induces increased bone turnover compared to a high intake of milk with a low-calcium diet. Thus, the trend towards a replacement of milk with cola and other soft drinks, which results in a low calcium intake, may negatively affect bone health as indicated by this short-term study.

http://www.ncbi.nlm.nih.gov/pubmed/15886860

European Journal Of Gastroenterology And Hepatology • July 2002

Gastric phytobezoars may be treated by nasogastric Coca-Cola lavage

Author information

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Abstract

Large gastric phytobezoars may occur in patients with gastric dysmotility disorders. Treatment options include dissolution with enzymes, endoscopic fragmentation with removal or aspiration, and surgery. We report our experience with nasogastric cola lavage therapy. Over an 8-year period, five consecutive patients were referred to our unit for endoscopic treatment of large gastric phytobezoars. They included one patient with lobectomy for lung cancer and four patients with diabetic gastroparesis. An initial attempt of endoscopic fragmentation and removal was unsuccessful. Patients were treated with 3 l of Coca-Cola nasogastric lavage over 12 h. Nasogastric lavage was very well tolerated by the patients. Complete phytobezoar dissolution was achieved in one session in all cases. There were no procedure-related complications. The dissolution of large gastric phytobezoars with cola nasogastric lavage is a safe, rapid and effective method. Patients may be treated in the medical ward, avoiding therapeutic endoscopy or surgery.

http://www.ncbi.nlm.nih.gov/pubmed/12169994

“when a complete diet was given, no physiological difference in time was observed, except in diarrhea ...”

The Journal Of Toxicology Sciences • November 1979

Deleterious effect of short-term exposure to Coca-Cola on rats

Tamura T, Fujii A, Kusaba H.

Abstract

Semiacute toxicity of cola fluid, Coca-Cola, conducting for approximately a month in rats, was studied. A trend of cariogenicity of Coca-Cola was strongly indicated. When the fluid was given ad libitum, decarbonized Coca-Cola and carbohydrate solution, consisted 8% of glucose and 3.5% of sugar and then adjusted pH to 2.4 with oxalic acid, were consumed 2 to 3 times greater than the control (water). A hyperuresis was observed as the result of great consumption of liquid, but no liver nor kidney degeneration was observed by histopathological examination. The diet consumption of the groups of Coca-Cola and carbohydrate solution was approximately a half of the control, water. However, when a complete diet was given, no physiological difference in time was observed, except in diarrhea and depression of hair gloss in Coca-Cola group.

Full text, PDF, graphs, charts with 13 references

https://www.jstage.jst.go.jp/article/jts1976/4/4/4_4_363/_pdf

Fuck Coca-Cola

People are taking the piss out of you *everyday.* They butt into your life, take a cheap shot at you and then disappear. They leer at you from tall buildings and make you feel **small.** They make flippant comments from buses that imply you're not sexy enough and that all the fun is happening somewhere else. They are on TV making your girlfriend feel inadequate. They have access to the most sophisticated technology the world has ever seen and they bully you with it. They are

The Advertisers

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CHAPTER TWENTY-NINE

Phytochemicals • Flavonoids

The Peer Review

Flavonoids are one of the largest nutrient families known to scientists, and include over 6,000 already-identified family members. Some of the best-known flavonoids include quercetin, kaempferol, catechins, and anthocyanidins.

Flavonoids are a remarkable group of phytonutrients that fall into the chemical category of polyphenols. They're perhaps most famous for their rich diversity of color-providing pigments including the deep blues of blueberries and rich reds of raspberries. As a group flavonoids are highly bioactive and play a wide variety of different roles in the health of plants, animals, and human health.

Flavonoids are best known for their antioxidant and anti-inflammatory health benefits as well as the support of the cardiovascular and nervous systems. Because they also help support detoxification of potentially tissue-damaging molecules, their intake has often, although not always, been associated with decreased risk of certain types of cancers, including lung and breast cancer. However, it is important to note that the amount of flavonoids required to provide the above health benefits is not certain, and there are some conflicting research findings in this regard.

Because many flavonoids—and especially those belonging to two flavonoid subgroups called flavonols and flavan-3-ols—can be effective in reducing free radical damage to cells and other components in body tissue, they provide antioxidant benefits. It is not clear, however, if we should be thinking about flavonoids as falling into the same category as more widely known antioxidant nutrients like vitamin C or vitamin E. Yet flavonoids appear to be critical elements of diet.

One reason for this is because their concentration in the bloodstream is so much lower. Another reason lies in the fact that many of the antioxidant functions of the flavonoids are not performed by the flavonoids themselves, but by forms of the flavonoids that have been altered by our metabolism. Even though we do not know all the details about the way flavonoids function as antioxidants, studies have documented better protection of certain cell types—for example, red blood cells—following consumption of flavonoid-rich foods. Blueberries, for example, have been repeatedly studied in this context for their flavonoid-related antioxidant benefits.

In this antioxidant context, it is also worth pointing out the potentially unique relationship between flavonoids and vitamin C. Recent studies have shown the ability of flavonoids to alter transport of vitamin C, as well as to alter function of an enzyme called ascorbate oxidase, which converts vitamin C into a non-vitamin form (monodehydroascorbate). While we do not yet know the full meaning of these relationships, it is clear that the transport and cycling of vitamin C is flavonoid related. This association makes sense since so many foods high in vitamin C are also high in flavonoids. Much of the research on flavonoids as anti-inflammatories has involved their ability to block the production of messaging molecules that promote inflammation. In metabolic terms, this activity of flavonoids in-

volves the inhibition of cyclo-oxygenase (COX) and lipoxygenase (LOX) enzymes. Not only have specific flavonoids (for example, quercetin) been shown to provide these benefits but so also have flavonoid-containing extracts from a variety of foods, spices, and herbs. In addition to the metabolic activities described above, food flavonoids have also been shown to suppress inflammatory signaling in another metabolic pathway called the nuclear factor kappa-B (NF-kB) pathway.

Not surprisingly, since many problems in the cardiovascular system involve problems with oxidative stress and inflammation, the antioxidant and anti-inflammatory benefits from food flavonoids provide direct support for this body system. In the bloodstream, flavonoids have been shown to help protect LDL cholesterol molecules from oxygen-related damage. This LDL protection, in turn, helps to lower risk of atherosclerosis. Flavonoids including rutin and hesperidin have also been shown to increase the strength and integrity of the blood vessel walls, lowering risk of blood vessel problems. In one study, adding a spice mix to a meal of beef—a mix that contained such flavonoid-rich herbs as oregano, rosemary, garlic, ginger, and black pepper—led to a significant improvement in vascular function over the next several hours. Yet herbs and spices are by no means the only foods studied in this regard; similar effects have been demonstrated for soy foods, chocolate, pomegranate juice, and grape juice.

Numerous flavonoids—including quercetin and rutin—have been shown to help prevent excessive clumping together of platelet cells that could otherwise lead to unwanted clogging of the blood vessels. This property of flavonoids is called an "anti-aggregatory" property, and it's yet another way in which these phytonutrients help support the cardiovascular system. In 2014, a research group looked at cardiovascular benefits related to the flavonoid content of fruits and vegetables. These researchers were able to determine that six total fruit and vegetable servings did a better job at protecting cardiovascular health than four total servings. They also decided upon six total servings of fruits-plus-vegetables as their *minimal* recommendation for heart health.

Protection of nerve cells from oxygen-based damage, and help during the slow and demanding process of nerve regeneration (outside of the brain and spinal cord), are both demonstrated benefits of flavonoid intake for the nervous system. There is some preliminary evidence that the onset of certain chronic neurodegenerative diseases—including age-related dementia and Alzheimer's disease—may be delayed when long-term intake of flavonoids has been strong. Because flavonoids may help to improve blood flow in the brain, there is also preliminary evidence to suggest the possibility of better brain functioning in some areas, including areas involving cognitive function.

In terms of their anti-cancer potential, research on flavonoids has been somewhat mixed. Due to their well-documented antioxidant and anti-inflammatory properties, flavonoids would be expected to lower risk of certain cancers since chronic oxidative stress and chronic unwanted inflammation can place cells at greater risk of becoming cancerous. Furthermore, because flavonoids are known to modify the body's detoxification pathways, it might be expected that flavonoids would help lower exposure to unwanted toxins that could pose increased cancer risk. In studies on animals and on isolated cell types, the above expectations seem to be fully met, with flavonoid intake improving detoxification, oxidative stress, unwanted inflammation, and initiation of cells into pre-cancerous states. However, in larger scale studies on humans and risk of human cancers, greater intake of flavonoids has not been consistently associated with decreased risk of cancer. To date, the strongest evidence appears to involve breast cancer and lung cancer where decreased risk is a more consistent finding.

Part of the mixed findings in this flavonoids-and-cancer area might involve the complex nature of flavonoids as a group. For example, it may be the case that certain subgroups of flavonoids are particularly helpful for lowering risk of certain types of cancer. It might also be the case that studies have had trouble accurately quantifying flavonoid intake. There are thousands and thousands of food flavonoids, and yet some studies have only focused on very select examples or limited types of foods.

Improved detoxification is a very likely benefit that we get from strong flavonoid intake; most researchers have concluded that strong flavonoid intake modified detoxification in a helpful way and decreases our risk of problems from unwanted toxins. A final potential health benefit is better regulation of cell cycles. Most cells in our body go through stages of activity where they rest, divide, or go into a self-dismantling and self-recycling process called apoptosis. In the health of all our body systems, it is important for these cell cycle stages to stay in balance. Ample intake of food flavonoids appears to promote these cell cycle balances, most likely through regulation of signaling that takes place between cells and their surroundings.

Flavonoids are a very large (more than 6,000 have been identified so far) and very diverse group of phytonutrients. The U.S. Department of Agriculture's (USDA) Flavonoid Database actually breaks down its flavonoid analyses into five of the basic flavonoid chemical subgroups, and it analyzes the best food choices in each of these subgroups. This approach to understanding the flavonoid content of food emphasizes the need to consume a wide variety of flavonoids that includes all of the different types. The five subcategories are: (1) flavonols (which include quercetin, kaempferol, myricetin, and isorhamnetin); (2) flavan-3-ols (which include catechins, epicatechins, gallocatechins, and theaflavins); (3) flavones (which include apigenin and luteolin); (4) flavonones (which include hesperetin, naringenin, and eriodictyol); and (5) anthocyanidins (which include cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin).

It's important to note that in the U.S. the largest single source of flavonoids is black and green tea, and that over half of all flavonoid intake comes from the flavan-3-ol subgroup that is so concentrated in tea; this subgroup includes catechins, epicatechins, gallocatechins, and theaflavins.

As you can see, it takes a variety of foods from a variety of different food groups to give you a good cross-section of flavonoid subcategories. The USDA estimates that in the U.S., daily total flavonoid consumption by the average adult is approximately 250-275 milligrams, with about half of total consumption coming in the form of flavan-3-ols from black and green tea.

The colorful reds, blues, and purples in berries are provided by their anthocyanidins, and that is why you find so many of these fruits listed in the anthocyanidin column. As a group of phytonutrients, flavonoids emphasize—in a way that is not as well emphasized by perhaps any other nutrient—how valuable fruits and vegetables are to our nourishment and everyday health.

You will lose some flavonoids from plant foods during prolonged storage. For example, onions stored at room temperature will lose about one quarter to one third of their original flavonoid content over six months, with most of the loss occurring in the first two weeks. As water-soluble nutrients, flavonoids can be lost through water contact, and in some cases, up to 80% of specific flavonoids can be lost into cooking water during the boiling of foods. Because many flavonoids provide visible colors in a food, loss of flavonoids during boiling can often be seen in a dulling of the food's colors. Color changes of this kind are one of the indicators of overcooking; if you boil or steam a food long enough to see its vibrant colors start to dull or disappear, you can be sure that you are losing too many valuable nutrients from the food, including its health-supportive flavonoids.

Flavonoids are susceptible to damage by heat, and as mentioned earlier, they are also susceptible to damage over prolonged periods of time. This issue of time brings us to the benefits of fresh fruits and vegetables, which are likely to be more flavonoid-rich the fresher they are at the time of purchase. The issue of heat is a caution against frying or lengthy cooking even in medium heats.

Flavonoids are often concentrated in the skins and outer portions of fruits and vegetables and these portions of the foods are excellent to consume. Due to risk of contamination on these outermost surfaces, you always want to wash the foods and gently scrub them with a vegetable brush. Of course, you can also reduce risk of contamination by purchasing certified organic foods. When you are storing flavonoid-rich foods, it is best not to damage their skins prior to storage, for example, by pre-cutting, pre-slicing, or pre-peeling and then placing in the refrigerator. They are best kept in whole, natural form until you are ready to consume them or prepare them for inclusion in a recipe.

As mentioned earlier, average consumption of flavonoids in the U.S. is far less than 1 gram per day (at about 250-275 milligrams), with black and green tea serving as the number one source of these phytonutrients. While we would classify this level of intake to be inadequate from a health standpoint, we don't have a good standard to use in determining optimal flavonoid amounts. There is no Dietary Reference Intake (DRI) for flavonoids and no Daily Value (DV); in addition, nutrient databases do no provide anywhere close to comprehensive information about the overall flavonoid content of foods. All of these limitations make statements about dietary deficiency somewhat tentative. However, from a common sense standpoint, let's say that a person consumed six vegetable and four fruit servings in a day, for a total of 10 vegetable-plus-fruit servings. Furthermore, let's say that all of these servings came from whole, natural foods. In this situation, a person's total flavonoid intake would be likely to fall somewhere near 1 gram (1,000 milligrams) or more. It is within this context that we consider average flavonoid intake in the U.S. to be inadequate. In addition, since a disproportional amount of U.S. flavo-

noids come from a single flavonoid subgroup (flavan-3-ols provided from black and green tea), there is likely to be flavonoid deficiency from the other subgroups given the pattern of flavonoid consumption in the U.S. Risk of dietary deficiency for flavonoids is basically synonymous with low dietary intake of whole, natural foods, and in particular, low intake of vegetables and fruits. By far your best way to ensure ample flavonoid intake is to maximize your intake of whole natural foods, including fresh, brightly colored vegetables and fruits whose flavonoid pigments provide them with their vibrant colors. This approach sounds simple, and it is, and it's a great method for increasing your flavonoid intake.

Most documented risks for flavonoid deficiency have already been discussed since they involve poor dietary intake. Overconsumption of processed foods, overcooking of foods, and underconsumption of fresh vegetables and fruits are the primary circumstances related to deficiency. Problems with the chewing of fresh foods can increase a person's flavonoid deficiency risk, especially if these foods are avoided in a meal plan due to chewing problems. Lack of appetite can also put a person at risk of deficiency, simply due to overall low intake. In studies of the overall U.S. population, inadequate intake of nutrients—including flavonoids—can be associated with poverty and general lack of access to fresh foods.

We are not aware of any evidence that dietary flavonoids can be directly toxic, even in meal plans that contain an abundance of fresh vegetables and fruits as well as an abundance of nuts, seeds, beans, legumes, and whole grains. When consumption of the foods above is very high, the total fiber content of the diet usually goes up dramatically. (In comparison to average fiber intake in the U.S., which averages about 16 grams per day, fiber intake in countries with high consumption of the foods above often exceeds 100 grams. So we would expect high flavonoid intake from whole natural foods to accompany diets high in dietary fiber, and we just do not see toxicity risks being associated with this type of dietary intake.

In addition, since flavonoids are water-soluble, we would expect them to follow a pattern associated with other water-soluble nutrients. That pattern involves lower risk of toxicity than is associated with fat-soluble nutrients, and in many cases, a decision by the National Academy of Sciences (NAS) not to establish a Tolerable Upper Intake Level (UL) for water-soluble vitamins like vitamin B1 or vitamin B2 when obtained from food. A similar decision might end up holding true for flavonoids as well.

There are currently no Dietary Reference Intakes (DRIs) from the National Academy of Sciences and there is no Daily Value (DV) from the U.S. Food and Drug Administration. However, as described earlier, our recommendation for optimal flavonoid intake is to focus on a whole, natural, fresh foods diet that provides ample servings of vegetables and fruits. When coupled with other flavonoid-rich foods—including nuts, seeds, beans, legumes, and whole grains—your flavonoid intake is likely to far surpass the current U.S. average level of approximately 250-275 milligrams, and may in fact get closer to a level of approaching 1 gram (1,000 milligrams).

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A New Database Facilitates Characterization of Flavonoid Intake, Sources, and Positive Associations with Diet Quality among US Adults

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Background

Epidemiologic studies demonstrate inverse associations between flavonoid intake and chronic disease risk. However, lack of comprehensive databases of the flavonoid content of foods has hindered efforts to fully characterize population intakes and determine associations with diet quality.

Objectives

Using a newly released database of flavonoid values, this study sought to describe intake and sources of total flavonoids and 6 flavonoid classes and identify associations between flavonoid intake and the Healthy Eating Index (HEI) 2010.

Conclusions

A new database that permits comprehensive estimation of flavonoid intakes in WWEIA, NHANES 2007–2008; identification of their major food/beverage sources; and determination of associations with dietary quality will lead to advances in research on relations between flavonoid intake and health. Findings suggest that diet quality, as measured by HEI, is positively associated with flavonoid intake.

Full text with 85 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4442120/

“Evidence-informed dietary priorities include increased fruits, nonstarchy vegetables, nuts, legumes, fish, vegetable oils, yogurt, and minimally processed whole grains; and fewer red meats, processed (eg, sodium-preserved) meats, and foods rich in refined grains, starch, added sugars, salt, and trans fat.

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Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review

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Abstract

Suboptimal nutrition is a leading cause of poor health. Nutrition and policy science have advanced rapidly, creating confusion yet also providing powerful opportunities to reduce the adverse health and economic impacts of poor diets. This review considers the history, new evidence, controversies, and corresponding lessons for modern dietary and policy priorities for cardiovascular diseases, obesity, and diabetes mellitus. Major identified themes include the importance of evaluating the full diversity of diet-related risk pathways, not only blood lipids or obesity; focusing on foods and overall diet patterns, rather than single isolated nutrients; recognizing the complex influences of different foods on long-term weight regulation, rather than simply counting calories; and characterizing and implementing evidence-based strategies, including policy approaches, for lifestyle change. Evidence-informed dietary priorities include increased fruits, nonstarchy vegetables, nuts, legumes, fish, vegetable oils, yogurt, and minimally processed whole grains; and fewer red meats, processed (eg, sodium-preserved) meats, and foods rich in refined grains, starch, added sugars, salt, and trans fat. More investigation is needed on the cardiometabolic effects of phenolics, dairy fat, probiotics, fermentation, coffee, tea, cocoa, eggs, specific vegetable and tropical oils, vitamin D, individual fatty acids, and diet-microbiome interactions. Little evidence to date supports the cardiometabolic relevance of other popular priorities: eg, local, organic, grass-fed, farmed/wild, or non-genetically modified. Evidence-based personalized nutrition appears to depend more on nongenetic characteristics (eg, physical activity, abdominal adiposity, gender, socioeconomic status, culture) than genetic factors. Food choices must be strongly supported by clinical behavior change efforts, health systems reforms, novel technologies, and robust policy strategies targeting economic incentives, schools and workplaces, neighborhood environments, and the food system. Scientific advances provide crucial new insights on optimal targets and best practices to reduce the burdens of diet-related cardiometabolic diseases.

http://www.ncbi.nlm.nih.gov/pubmed/26746178

“It was found that the application of the Oregano Essential Oil in meat is effective in inhibiting Salmonella enteritidis and Escherichia coli. Microbial load can be controlled using either synthetic or natural preservatives. Particular interest has been focused on the potential application of plant essential oils as safer additives for meat. However, there is no applied research about the use of essential oils during the meat drying process. It was found that the application of the Oregano Essential Oil in meat is effective in inhibiting Salmonella enteritidis and Escherichia coli.”

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The effect of oregano essential oil on microbial load and sensory attributes of dried meat

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Abstract

BACKGROUND

Microbial load can be controlled using either synthetic or natural preservatives. Particular interest has been focused on the potential application of plant essential oils as safer additives for meat. However, there is no applied research about the use of essential oils during the meat drying process. This study is focused on enhancing the meat drying process, a value-added dried meat product by using oregano essential oil (OEO) to inhibit the growth of bacteria, and the sensorial response from assessors are presented.

RESULTS

It was found that the application of the OEO in meat is effective in inhibiting Salmonella enteritidis and Escherichia coli. After 6 hours of drying at 55 °C, 2 ml (0.038 ml l-1 air vapours) and 1.5 ml (0.028 ml l-1 air vapours) of OEO are considered the minimal inhibitory concentrations (MICs) against S. enteritidis and E. coli, respectively. The samples treated with 0.75 ml of OEO are more attractive for consuming compare to the original one and with a higher concentration of OEO the sensory quality of the food is affected.

CONCLUSIONS

A value-added meat product by using oregano essential oil for enhancement the food safety and an acceptable sensorial response from consumers is presented.

http://www.ncbi.nlm.nih.gov/pubmed/26917258

“The fruits of X. americana showed considerable amounts of bioactive compounds, as well as antioxidant activity and antioxidant enzymes. The fruits at green maturity stage showed higher content of yellow flavonoids (22.07 mg/100g), anthocyanins (1.92 mg/100 g), polyphenols (3051.62 mg/100 g), starch (4.22%), antioxidant activity (489.40 g fruit/g DPPH and 198.77 μmol Trolox/g) and activity of antioxidant enzymes; the antioxidant activity allocated to the fruit was shown to be related to the contents of extractable polyphenols, yellow flavonoids, total anthocyanins and antioxidant enzymes.”

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Bioactive compounds and antioxidant potential fruit of Ximenia americana L

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Abstract

The caatinga ecoregion in northeast Brazil presents a wide variety in plant species. However, the potential of these species as a source of energy, carbohydrates, vitamins, minerals and bioactive properties beneficial to health is still unknown. Among these species we can find the wild plum (Ximenia americana). Due to its various phytotherapeutic properties and absence of studies on the chemical composition of the fruit this article aimed to evaluate the bioactive compounds and antioxidant potential of the X. americana in different stages of maturation. The fruits of X. americana showed considerable amounts of bioactive compounds, as well as antioxidant activity and antioxidant enzymes. The fruits at green maturity stage showed higher content of yellow flavonoids (22.07 mg/100g), anthocyanins (1.92 mg/100 g), polyphenols (3051.62 mg/100 g), starch (4.22%), antioxidant activity (489.40 g fruit/g DPPH and 198.77 μmol Trolox/g) and activity of antioxidant enzymes; the antioxidant activity allocated to the fruit was shown to be related to the contents of extractable polyphenols, yellow flavonoids, total anthocyanins and antioxidant enzymes.

http://www.ncbi.nlm.nih.gov/pubmed/26304450

“The presented results support traditional use of rose hips and their fruit preserves as food with health and nutritional benefits.”

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Comparative study of biological activities and phytochemical composition of two rose hips and their preserves: Rosa canina L. and Rosa arvensis Huds

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Abstract

The aim of this study was to compare phenolic profile, vitamin C content, antioxidant, anti-inflammatory and cytotoxic activity of rose hips and the preserves (purée and jam) of two Rosa species: renowned Rosa canina L. and unexplored Rosa arvensis Huds. The liquid chromatography-tandem mass spectrometry analysis of 45 phenolics resulted in quantification of 14 compounds, with quercitrin, gallic and protocatechuic acids as the most dominant. High antioxidant potential of R. canina and a moderate activity of R. arvensis extracts were determined through several assays. Purée of both species and methanol extract of air-dried R. canina hips showed some anti-inflammatory (cyclooxygenase-1 and 12-lipooxygense inhibition potency) activity. Purée of R. canina exerted cytotoxic activity only against the HeLa cell line among several others (HeLa, MCF7, HT-29 and MRC-5). The presented results support traditional use of rose hips and their fruit preserves as food with health and nutritional benefits.

http://www.ncbi.nlm.nih.gov/pubmed/26304428

“The **low dose of parsley** 10 g/kg/day exhibited significant effects in neutralizing and reducing the deleterious changes due to Cd exposure during pregnancy on the behavioral activities, neurotransmitters, oxidative stress, and brain neurons morphology of the mice newborns.”

Oxidative Medicine and Cellular Longevity • February 2016

Protective Effect of Parsley Juice (Petroselinum crispum, Apiaceae) against Cadmium Deleterious Changes in the Developed Albino Mice Newborns (Mus musculus) Brain

Author information

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Abstract

Parsley was used as a probe of the current experiment to prevent the behavioral, morphological and biochemical changes in the newborn brain following the administration of cadmium (Cd) to the pregnant mice. The nonanesthetized pregnant mice were given daily parsley juice (Petroselinum crispum) at doses of 20 mg/kg and 10 mg/kg. Pregnant mothers were given Cd at a dose of 30 mg/kg divided into 3 equal times. The newborns have been divided into 6 groups: Group A, mothers did not take treatment; Groups B and C, mothers were treated with low and high dose of parsley, respectively; Group D, mothers were treated only with Cd (perinatal intoxication); Groups E and F, mothers were treated with Cd doses and protected by low and high doses of parsley, respectively. Light microscopy showed that Cd-induced neuronal degeneration by chromatolysis and pyknosis in the brain regions. The low dose of parsley 10 g/kg/day exhibited significant effects in neutralizing and reducing the deleterious changes due to Cd exposure during pregnancy on the behavioral activities, neurotransmitters, oxidative stress, and brain neurons morphology of the mice newborns.

Full text, graphs, charts and 56 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4761399/

“This study provides data on nutrients, bioactive compounds and antioxidant activities of indigenous and popular durian varieties that could be used for consumer education as well as for incorporation into the food composition databases.”

Food Chemistry • February 2016

Nutrients and bioactive compounds in popular and indigenous durian (Durio zibethinus murr.)

Author information

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Abstract

This study identified nutrients, fatty acids, bioactive compounds and antioxidant activities of two popular varieties (Mon-thong, Cha-ni) and two indigenous varieties (Kra-dum and Kob-ta-kam) of durian. Each of variety was collected from 3 gardens in Nonthaburi province, Thailand. At optimal ripeness, the edible part was separated, homogenised or freeze dried, as fresh or dry samples for further analysis using standard methods. All durian varieties contained a considerable amount of dietary fibre (7.5-9.1g/100g dry matter, DM) and high amounts of carbohydrate and sugar (62.9-70.7g and 47.9-56.4g/100g DM respectively). Cha-ni, Kra-dum and Kob-ta-kam varieties had monounsaturated (MUFA) (6.1-7.8g/100g DM)>saturated (SFA) (4.2-5.7g/100g DM)>polyunsaturated fatty acid (PUFA) (0.8-1.5g/100g DM), whereas the Mon-thong variety had SFA>MUFA>PUFA (5.1, 4.0, 1.1g/100g DM, respectively). The Kob-ta-kam variety showed greater potential for health benefits in terms of carotenoids and ß-carotene (2248µg and 1202µg/100g DM respectively). Phenolic compounds and antioxidant capacity were not significantly different among each variety, though the Cha-ni variety had the lowest. This study provides data on nutrients, bioactive compounds and antioxidant activities of indigenous and popular durian varieties that could be used for consumer education as well as for incorporation into the food composition databases.

http://www.ncbi.nlm.nih.gov/pubmed/26433306

“... routine use of probiotics cannot be supported on the basis of current scientific evidence. Safety of probiotics is also a concern; rarely, probiotics may cause bacteremia, fungemia, and sepsis in immunocompromised critically ill children.”

F1000 Research • March 2016

Probiotics in critically ill children

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Abstract

Gut microflora contribute greatly to immune and nutritive functions and act as a physical barrier against pathogenic organisms across the gut mucosa. Critical illness disrupts the balance between host and gut microflora, facilitating colonization, overgrowth, and translocation of pathogens and microbial products across intestinal mucosal barrier and causing systemic inflammatory response syndrome and sepsis. Commonly used probiotics, which have been developed from organisms that form gut microbiota, singly or in combination, can restore gut microflora and offer the benefits similar to those offered by normal gut flora, namely immune enhancement, improved barrier function of the gastrointestinal tract (GIT), and prevention of bacterial translocation. Enteral supplementation of probiotic strains containing either Lactobacillus alone or in combination with Bifidobacterium reduced the incidence and severity of necrotizing enterocolitis and all-cause mortality in preterm infants. Orally administered Lactobacillus casei subspecies rhamnosus, Lactobacillus reuteri, and Lactobacillus rhamnosus were effective in the prevention of late-onset sepsis and GIT colonization by Candida in preterm very low birth weight infants. In critically ill children, probiotics are effective in the prevention and treatment of antibiotic-associated diarrhea. Oral administration of a mix of probiotics for 1 week to children on broad-spectrum antibiotics in a pediatric intensive care unit decreased GIT colonization by Candida, led to a 50% reduction in candiduria, and showed a trend toward decreased incidence of candidemia. However, routine use of probiotics cannot be supported on the basis of current scientific evidence. Safety of probiotics is also a concern; rarely, probiotics may cause bacteremia, fungemia, and sepsis in immunocompromised critically ill children. More studies are needed to answer questions on the effectiveness of a mix versus single-strain probiotics, optimum dosage regimens and duration of treatment, cost effectiveness, and risk-benefit potential for the prevention and treatment of various critical illnesses.

Full text, graphs, charts and 83 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4813632/

“These results suggest that osmotin or osmotin-based therapeutic agents might be potential candidates for Alzheimer’s disease treatment.”

Molecular Psychiatry • March 2016

Novel osmotin inhibits SREBP2 via the AdipoR1/AMPK/SIRT1 pathway to improve Alzheimer’s disease neuropathological deficits

Author information

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Abstract

Extensive evidence has indicated that a high rate of cholesterol biogenesis and abnormal neuronal energy metabolism play key roles in Alzheimer’s disease (AD) pathogenesis. Here, for we believe the first time, we used osmotin, a plant protein homolog of mammalian adiponectin, to determine its therapeutic efficacy in different AD models. Our results reveal that osmotin treatment modulated adiponectin receptor 1 (AdipoR1), significantly induced AMP-activated protein kinase (AMPK)/Sirtuin 1 (SIRT1) activation and reduced SREBP2 (sterol regulatory element-binding protein 2) expression in both in vitro and in vivo AD models and in Adipo-/- mice. Via the AdipoR1/AMPK/SIRT1/SREBP2 signaling pathway, osmotin significantly diminished amyloidogenic Aß production, abundance and aggregation, accompanied by improved pre- and post-synaptic dysfunction, cognitive impairment, memory deficits and, most importantly, reversed the suppression of long-term potentiation in AD mice. Interestingly, AdipoR1, AMPK and SIRT1 silencing not only abolished osmotin capability but also further enhanced AD pathology by increasing SREBP2, amyloid precursor protein (APP) and ß-secretase (BACE1) expression and the levels of toxic Aß production. However, the opposite was true for SREBP2 when silenced using small interfering RNA in APPswe/ind-transfected SH-SY5Y cells. Similarly, osmotin treatment also enhanced the non-amyloidogenic pathway by activating the ß-secretase gene that is, ADAM10, in an AMPK/SIRT1-dependent manner. These results suggest that osmotin or osmotin-based therapeutic agents might be potential candidates for AD treatment.

http://www.ncbi.nlm.nih.gov/pubmed/27001618

Genetics And Molecular Biology • March 2016

Protective effects of acerola juice on genotoxicity induced by iron in vivo

Author information

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Abstract

“Metal ions such as iron can induce DNA damage by inducing reactive oxygen species (ROS) and oxidative stress. Vitamin C is one of the most widely consumed antioxidants worldwide, present in many fruits and vegetables, especially in Malpighia glabra L., popularly known as acerola, native to Brazil. Acerola is considered a functional fruit due to its high antioxidant properties and phenolic contents, and therefore is consumed to prevent diseases or as adjuvant in treatment strategies. Here, the influence of ripe and unripe acerola juices on iron genotoxicity was analyzed in vivo using the comet assay and micronucleus test. The comet assay results showed that acerola juice exerted no genotoxic or antigenotoxic activity. Neither ripe nor unripe acerola juices were mutagenic to animals treated with juices, in micronucleus test. However, when compared to iron group, the pre-treatment with acerola juices exerted antimutagenic activity, decreasing significantly micronucleus mean values in bone marrow. Stage of ripeness did not influence the interaction of acerola compounds with DNA, and both ripe and unripe acerola juices exerted protective effect over DNA damage generated by iron.”

Full text, graphs, charts and 35 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4807388/

Food Chemistry • March 2016

Cooking influence on physico-chemical fruit characteristics of eggplant (Solanum melongena L.)

Author information

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Abstract

"Physico-chemical traits of three eggplant genotypes ("Tunisina", "Buia" and "L 305") were evaluated before and after two cooking treatments (grilling and boiling). Different genotypes revealed different changes after cooking, with "Tunisina" showing a better retention of phytochemicals with respect to other two genotypes. The main physical phenomena were water loss during grilling, and dry matter loss after boiling. Chlorogenic acid, the main phenolic in eggplant, resulted higher in grilled samples, while delphinidin glycosides resulted more retained in boiled samples. Glycoalkaloids, thiols and biogenic amines were generally stable, while 5-hydroxy-methyl-furfural was found only in grilled samples. Interestingly, Folin-Ciocalteu index and free radical scavenging capacity, measured with three different assays, were generally increased after cooking, with a greater formation of antioxidant substances in grilled samples. NMR relaxation experiments clarified the hypothesis about the changes of eggplant compounds in terms of decomposition of larger molecules and production of small ones after cooking."

http://www.ncbi.nlm.nih.gov/pubmed/26471625

Food Chemistry • March 2016

Assessment of the differences in the physical, chemical and phytochemical properties of four strawberry cultivars using principal component analysis

Author information

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Abstract

“The worldwide established strawberry cultivar ‘Albion’ and three recently introduced cultivars in Europe: ‘Monterey’, ‘Capri’, and ‘Murano’, grown hydroponically, were studied to ascertain the influence of cultivar and harvesting date on the physical, chemical, antioxidant and phytochemical properties of their fruits. Interrelationships of investigated parameters and these cultivars were investigated by the statistical approach of principal component analysis (PCA). Results indicated that cultivar had a more significant effect on the analyzed parameters than harvesting date. Thus grouping of the variables in a PCA plot indicated that each cultivar has specific characteristics important for consumer or industrial use. Cultivar ‘Monterey’ was the richest in phytochemical contents and consequently in antioxidant activity, ‘Albion’ showed the highest contents of total soluble solids, titratable acidity content and ascorbic acid, ‘Capri’ had the highest value of firmness, while ‘Murano’ had lighter color in comparison to others. Potential use of these cultivars has been assessed according to these important measured attributes.”

http://www.ncbi.nlm.nih.gov/pubmed/26471624

Journal Of Medicinal Food • March 2016

Phytochemical Constituents and Antioxidant and Antimicrobial Activity of Selected Plants Used Traditionally as a Source of Food

Author information

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Abstract

"Many indigenous plants have also been used as a source of food and medicine in many African rural communities in the past. The study investigated the antimicrobial activity, phytochemical constituent, and antioxidant activity of selected traditional plants used traditionally as a source of food and medicine. The methanol and water extracts of different plant parts were analyzed for phytochemicals using standard phytochemical screening reagents while the broth microdilution assays were used to analyze antimicrobial activities. Alkaloids, phenols, flavonoids, saponins, tannins, and terpenes were found in one or more of the plant extracts, and all the plant extracts demonstrated scavenging activities. The back extracts of Sclerocarya birrea and the leaf extracts of Garcinia livingstonei exhibit the best antioxidant activities, while the water and methanol back extracts of S. birrea and G. livingstonei were the most active against all the tested foodborne bacteria."

http://www.ncbi.nlm.nih.gov/pubmed/26987025

Pediatric Allergy And Immunology • April 2016

How relevant is panallergen sensitisation in the development of allergies?

Author information

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Abstract

“Panallergens comprise various protein families of plant as well as animal origin and are responsible for wide IgE cross-reactivity between related and unrelated allergenic sources. Such cross-reactivities include reactions between various pollen sources, pollen and plant-derived foods as well as invertebrate-derived inhalants and foodstuff. Here we provide an overview on the most clinically relevant panallergens from plants (profilins, polcalcins, non-specific lipid transfer proteins, pathogenesis-related protein family 10 members) and on the prominent animal-derived panallergen family, topomyosins. In addition, we explore the role of panallergens in the sensitisation process and progress of the allergic disease. Emphasis is given on epidemiological aspects of panallergen sensitisation and clinical manifestations. Finally, the issues related to diagnosis and therapy of patients sensitised to panallergens is outlined and the use of panallergens as predictors for cross-reactive allergy and as biomarkers for disease severity is discussed.”

http://www.ncbi.nlm.nih.gov/pubmed/27129102

“Therefore, the present article aims at critically reviewing the available literature on the beneficial effects of R. rosea on as a therapeutic strategy for the treatment of Alzheimer’s disease and other neurodegenerative diseases where oxidative stress plays a major role in disease development and progression.”

Phytotherapy Research • April 2016

Rhodiola rosea L. and Alzheimer’s Disease: From Farm to Pharmacy

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Abstract

Rhodiola rosea L. (roseroot) is a common member of the family Crassulaceae, known as one of the most important popular medicinal plants in the northern region of Europe. The roots of R. rosea possess a wide range of pharmacological activities such as antioxidant, antiinflammatory, anticancer, cardioprotective, and neuroprotective effects that are because of the presence of different phytochemicals such as phenols and flavonoids. In addition, the presence of salidroside, rosavins, and p-tyrosol are responsible for its beneficial effects for the treatment of on depression, fatigue, and cognitive dysfunction. A plethora of studies report that R. rosea has potent neuroprotective effects through the suppression of oxidative stress, neuroinflammation, and excitotoxicity in brain tissues and antagonism of oncogenic p21-activated kinase. However, to our knowledge, no review articles have been published addressing the neuroprotective effects of R. rosea. Therefore, the present article aims at critically reviewing the available literature on the beneficial effects of R. rosea on as a therapeutic strategy for the treatment of Alzheimer’s disease and other neurodegenerative diseases where oxidative stress plays a major role in disease development and progression. We also discuss the cultivation, phytochemistry, clinical impacts, and adverse effects of R. rosea to provide a broader insight on the therapeutic potential for this plant.

http://www.ncbi.nlm.nih.gov/pubmed/27059687

Molecules • May 2016

In Vitro Antioxidant, Anti-Diabetes, Anti-Dementia, and Inflammation Inhibitory Effect of Trametes pubescens Fruiting Body Extracts

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Abstract

Trametes pubescens, white rot fungus, has been used for folk medicine in Asian countries to treat ailments such as cancer and gastrointestinal diseases. This study was initiated to evaluate the in vitro antioxidant, anti-diabetes, anti-dementia, and anti-inflammatory activities of T. pubescens fruiting bodies. The 1,1-diphenyl-2-picryl-hydrazyl (DPPH) free radical scavenging activities of T. pubescens methanol (ME) and hot water (HWE) extracts (2.0 mg/mL) were comparable to butylated hydroxytoluene (BHT), the positive control. However, the chelating effects of ME and HWE were significantly higher than that of BHT. The HWE (6 mg/mL) also showed comparable reducing power to BHT. Eleven phenol compounds were detected by high performance liquid chromatography (HPLC) analysis. The ß-amylase and ß-glucosidase inhibitory activities of the ME and HWE of the mushroom were lower than Acarbose, the standard reference; however, the inhibitory effects of the mushroom extracts at 2.0 mg/mL were moderate. The acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory effects of ME and HWE were moderate and comparable with galanthamine, the standard drug to treat early stages of Alzheimer's disease (AD). The ME had a neuroprotective effect against glutamate-induced PC-12 cell cytotoxicity at the concentration range of 2-40 μg/mL. The mushroom extracts also showed inflammation inhibitory activities such as production of nitric oxide (NO) and expression of inducible nitric oxide synthase (iNOS) in lipopolysaccharide (LPS)-induced murine macrophage-like cell lines (RAW 264.7) and significantly suppressed the carrageenan-induced rat paw-edema. Therefore, fruiting body extracts of T. pubescens demonstrated antioxidant related anti-diabetes, anti-dementia and anti-inflammatory activities.

Full text, graphs, charts and 57 references with downloadable PDF link in left column

http://www.mdpi.com/1420-3049/21/5/639/htm

“The results showed that the rapeseed antitumor peptide RSP-4-3-3 could significantly change the morphological features of the HepG2 cells in vitro and cause apoptosis, thus inhibiting the proliferation of the HepG2 cells.”

Food Function • May 2016

Separation and purification of an anti-tumor peptide from rapeseed (Brassica campestris L.) and the effect on cell apoptosis

Author information

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Abstract

Rapeseed peptides were prepared by means of the combined methods of the laboratory bacteria enzyme synergy and the solid-state fermentation of rapeseed meal. The rapeseed peptides were separated and purified with the tumor cell in vitro anti-proliferative activity as an index. Moreover, a kind of rapeseed peptide component RSP-4-3-3 (rapeseed anti-tumor peptide RSP-4-3-3) with high activity was selected. Furthermore, by using reversed-phase high performance liquid chromatography (RP-HPLC) coupled with electrospray ionization mass spectrometry (ESI-MS/MS), the analysis result of its possible amino acid sequence showed that it was Trp-Thr-Pro (408.2 Da). Inverted microscope observation technology and western blot experiments were applied to explore the antitumor impact of the rapeseed peptide RSP-4-3-3 on tumor cells. The results showed that the rapeseed antitumor peptide RSP-4-3-3 could significantly change the morphological features of the HepG2 cells in vitro and cause apoptosis, thus inhibiting the proliferation of the HepG2 cells.

http://www.ncbi.nlm.nih.gov/pubmed/27116475

International Immunopharmacology • May 2016

Anti-inflammatory effects of royal poinciana through inhibition of toll-like receptor 4 signaling pathway

Author information

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Abstract

Inflammation is part of the non-specific immune response that occurs in reaction to any type of bodily injury. In some disorders the inflammatory process, which under normal conditions is self-limiting, becomes continuous and chronic inflammatory diseases develop subsequently including cardiovascular diseases, diabetes, cancer etc. Barks of Delonix regia is used traditionally in the treatment of inflammatory diseases. Therefore, in this study we evaluated the therapeutic potential of D. regia ethanol extract and its active constituent ß-Elemene with special interest in inflammation model using standard in vivo anti-inflammatory models: Carrageenan-induced paw edema, Cotton pellet granuloma, and Acetic acid-induced vascular permeability. To explicate the mechanism of action for the possible anti-inflammatory activity, we determined the level of major inflammatory mediators (NO, iNOS, COX-2-dependent prostaglandin E2 or PGE2), and pro-inflammatory cytokines (TNF-a, IL-1b, IL-6, and IL-12). Additionally, we determined the toll-like receptor 4 (TLR4), Myeloid differentiation primary response gene 88 (MyD88), by mRNA expression in drug treated LPS-induced murine macrophage model. To explore the mechanism of anti-inflammatory activity, we evaluated expression of c-Jun N-terminal kinases (JNK), nuclear factor kappa-B cells (NF-kB), and NF-kB inhibitor alpha (IK-Ba). Furthermore, we determined the acute and sub-acute toxicity of D. regia extract in BALB/c mice. This study established a significant anti-inflammatory activity of D. regia extract and ß-Elemene along with the inhibition of TNF-a, IL-1b, IL-6 and IL-12 expressions. Further, the expression of TLR4, NF-kBp65, MyD88, iNOS and COX-2 molecules were reduced in drug-treated groups, but not in the LPS-stimulated untreated or control groups, Thus, our results collectively indicated that the D. regia extract and ß-Elemene can efficiently inhibit inflammation.

http://www.ncbi.nlm.nih.gov/pubmed/26971223

Nutrients • June 2016

Isoflavones: Anti-Inflammatory Benefit and Possible Caveats

Author information

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Abstract

“Inflammation, a biological response of body tissues to harmful stimuli, is also known to be involved in a host of diseases, such as obesity, atherosclerosis, rheumatoid arthritis, and even cancer. Isoflavones are a class of flavonoids that exhibit antioxidant, anticancer, antimicrobial, and anti-inflammatory properties. Increasing evidence has highlighted the potential for isoflavones to prevent the chronic diseases in which inflammation plays a key role, though the underlying mechanisms remain unclear. Recently, some studies have raised concerns about isoflavones induced negative effects like carcinogenesis, thymic involution, and immunosuppression. Therefore, this review aims to summarize the anti-inflammatory effects of isoflavones, unravel the underlying mechanisms, and present the potential health risks.”

Full text with 141 references

Download the PDF: http://www.mdpi.com/2072-6643/8/6/361

International Journal Of Biological Macromolecules • July 2016

Antiviral activity of glycoprotein GP-1 isolated from Streptomyces kanasensis ZX01

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Abstract

“Plant virus diseases have seriously damaged global food security. However, current antiviral agents are not efficient enough for the requirement of agriculture production. So, developing new efficient and nontoxic antiviral agents is imperative. GP-1, from Streptomyces kanasensis ZX01, is a new antiviral glycoprotein, of which the antiviral activity and the mode of action against Tobacco mosaic virus (TMV) were investigated in this study. The results showed that GP-1 could fracture TMV particles, and the infection and accumulation of TMV in host plants were inhibited. Moreover, GP-1 could induce systematic resistance against TMV in the host, according to the results of activities of defensive enzymes increasing, MDA decreasing and overexpression of pathogenesis-related proteins. Furthermore, GP-1 could promote growth of the host plant. In conclusion, GP-1 showed the ability to be developed as an efficient antiviral agent and a fertilizer for agriculture.”

http://www.ncbi.nlm.nih.gov/pubmed/27091231

“Pectin-OEO coatings showed antifungal effect and increased the antioxidant activity without negative effects on the sensorial acceptability of tomatoes.”

Journal Of Science, Food And Agriculture • August 2016

Oregano (Lippia graveolens) essential oil added within pectin edible coatings prevents fungal decay and increases the antioxidant capacity of treated tomatoes

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Abstract

BACKGROUND

Tomato is a fruit widely consumed due to its flavor and nutritional value; however, it is susceptible to fungi contamination. Oregano essential oil (OEO) is a fungicide whose constituents are volatile; therefore, their incorporation within edible coatings can protect them and maintain their efficacy. In this context, this study evaluated the effect of OEO applied within pectin coatings on the inhibition of Alternaria alternata growth, antioxidant content and sensorial acceptability of tomatoes.

RESULTS

The major volatile compounds of OEO were carvacrol (47.41%), p-cymene (26.44%) and thymol (3.02%). All the applied OEO concentrations (15.7, 25.9 and 36.1 g L(-1)) inhibited the in vitro growth of A. alternata, whereas the in vivo effective concentrations were 25.9 and 36.1 g L(-1) . Additionally, there was an increment of total phenols and antioxidant activity in coated tomatoes compared to controls. Aroma acceptability of tomatoes was not affected by the pectin-OEO coating; additionally, the pectin, pectin-OEO 15.7 g L(-1) treatments and control tomatoes showed higher flavor acceptability than those coated with pectin-OEO 25.9 and 36.1 g L(-1) .

CONCLUSION

Pectin-OEO coatings showed antifungal effect and increased the antioxidant activity without negative effects on the sensorial acceptability of tomatoes.

http://www.ncbi.nlm.nih.gov/pubmed/26676868

Anticancer Agents In Medicinal Chemistry • January 2015

Anticancer agents derived from natural cinnamic acids

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Abstract

"Cancer is the most dangerous disease that causes deaths all over the world. Natural products have afforded a rich source of drugs in a number of therapeutic fields including anticancer agents. Many significant drugs have been derived from natural sources by structural optimization of natural products. Cinnamic acid has gained great interest due to its antiproliferative, antioxidant, antiangiogenic and antitumorigenic potency. Currently it has been observed that cinnamic acid and its analogs such as caffeic acid, sinapic acid, ferulic acid, and isoferulic acid display various pharmacological activities, such as immunomodulation, anti-inflammation, anticancer and antioxidant. They have served to be the major sources of potential leading anticancer compounds. In this review, we focus on the anticancer potency of cinnamic acid derivatives and novel strategies to design these derivatives. We hope this review will be useful for researchers who are interested in developing anticancer agents."

http://www.ncbi.nlm.nih.gov/pubmed/25634446

“Greater healthful food variety was associated with lower odds of Metabolic Syndrome and some Metabolic Syndrome components in the total population, Non-Hispanic White adults, and Non-Hispanic Black adults.”

Journal Of Nutrition • March 2015

Greater healthful food variety as measured by the US Healthy Food Diversity index is associated with lower odds of metabolic syndrome and its components in US adults

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Abstract

BACKGROUND
Consuming a wider variety of nutrient-dense foods may promote adherence to healthful dietary patterns, leading to improved dietary quality and enhanced metabolic health.

OBJECTIVE
We used the US Healthy Food Diversity (HFD) index to simultaneously measure dietary variety, quality, and proportionality, hypothesizing a priori that race/ethnicity may moderate associations between diet and health.

METHODS
A representative sample of adults (n = 7470) aged 20+ y with two 24-h recalls and complete outcome data from the cross-sectional NHANES 2003-2006 were selected. US HFD values were generated using a previously validated equation with a theoretical range from 0 to nearly 1, with higher scores indicative of more varied diets with a higher proportion of healthful food groups. Metabolic syndrome (MetS) was defined using the most recent harmonized definition. Survey-weighted multivariable linear and logistic regression, adjusted for demographic factors, smoking, energy, screen time, and leisure activity, were used to compute means and ORs (95% CIs).

RESULTS
Adults in the third vs. first US HFD tertile had 21% lower odds of MetS [OR (95% CI): 0.79 (0.64, 0.98)] as well as lower odds of hypertension [0.83 (0.70, 0.995] and elevated waist circumference [0.75 (0.66, 0.86] after multivariable adjustment (P-trend < 0.05). The age- and sex-adjusted odds of low serum HDL cholesterol and impaired fasting plasma glucose (P-trend < 0.05) were lower in the highest vs. lowest US HFD tertile but attenuated with multivariable adjustment (P = 0.06 and 0.22, respectively). Notably, the US HFD index was only protective against adiposity among non-Hispanic white (NHW) and non-Hispanic black (NHB) adults, and MetS associations were driven by NHW adults. No associations were observed among Hispanic adults for any MetS components.

CONCLUSIONS
Greater healthful food variety was associated with lower odds of MetS and some MetS components in the total population, NHW adults, and NHB adults. This study provides preliminary evidence that healthful food diversity may protect against MetS and highlights the need for longitudinal and experimental research.

Full text, graphs, charts and 52 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4336534/

“The Lemon Grass Oil toxicity mechanism was analyzed using qPCR and electron microscopy. Out of 370 genes, 57 genes (15.4%) were significantly up (34, 9.1%) or down (23, 6.2%) regulated, with the most upregulated gene gsta3 (200-fold) and the most affected pathway being oxidative stress. Lemon Grass Oil induced damage of mitochondria, phospholipid accumulation and lack of a brush border.”

Toxicology In Vitro • March 2015

In vitro safety assessment of food ingredients in canine renal proximal tubule cells

Author information

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Abstract

In vitro models are useful tools to initially assess the toxicological safety hazards of food ingredients. Toxicities of cinnamaldehyde (CINA), cinnamon bark oil, lemongrass oil (LGO), thymol, thyme oil (TO), clove leaf oil, eugenol, ginger root extract (GRE), citric acid, guanosine monophosphate, inosine monophosphate and sorbose (SORB) were assessed in canine renal proximal tubule cells (CPTC) using viability assay and renal injury markers. At LC50, CINA was the most toxic (0.012mg/ml), while SORB the least toxic (>100mg/ml). Toxicities (LC50) of positive controls were as follows: 4-aminophenol (0.15mg/ml in CPTC and 0.083mg/ml in human PTC), neomycin (28.6mg/ml in CPTC and 27.1mg/ml in human PTC). XYL displayed lowest cytotoxic potency (LC50=82.7mg/ml in CPTC). In vivo renal injury markers in CPTC were not significantly different from controls. The LGO toxicity mechanism was analyzed using qPCR and electron microscopy. Out of 370 genes, 57 genes (15.4%) were significantly up (34, 9.1%) or down (23, 6.2%) regulated, with the most upregulated gene gsta3 (200-fold) and the most affected pathway being oxidative stress. LGO induced damage of mitochondria, phospholipid accumulation and lack of a brush border. Viability assays along with mechanistic studies in the CPTC model may serve as a valuable in vitro toxicity screening tool.

http://www.ncbi.nlm.nih.gov/pubmed/25458622

[While Pistacia vera L. looks promising with inhibition of 54.2% ...]

“On the other hand, BHA, BHT, ß-tocopherol and trolox, pure antioxidant compounds, indicated inhibition of 80.3%, 73.5%, 36.2% and 72.0%... ”

Journal Of Enzyme Inhibition And Medical Chemistry • April 2015

Pistachio (Pistacia vera L.) gum: a potent inhibitor of reactive oxygen species

Author information

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Abstract

In the present study, in order to evaluate antioxidant and radical scavenging properties of Pistachio gum (P-Gum), different bioanalytical methods such as DPPH(•) scavenging activity, DMPD(•+) radical scavenging activity, total antioxidant activity determination by ferric thiocyanate, reducing ability Fe(3+)-Fe(2+) transformation, Cuprac and FRAP assays, O2(•-) scavenging by riboflavin-methionine-illuminate system and ferrous ions (Fe(2+)) chelating activities by 2,2’-bipyridyl reagent were performed separately. P-Gum inhibited 54.2% linoleic acid peroxidation at 10 µg/ml concentration. On the other hand, BHA, BHT, ß-tocopherol and trolox, pure antioxidant compounds, indicated inhibition of 80.3%, 73.5%, 36.2% and 72.0% on peroxidation of linoleic acid emulsion at the same concentration, respectively. In addition, all of sample had an effective DPPH(•), DMPD(•+) and O2(•-) scavenging, Fe(3+) reducing power by Fe(3+)-Fe(2+) transformation and FRAP assay, Cu(2+) reducing ability by Cuprac method and Fe(2+) chelating activities.

http://www.ncbi.nlm.nih.gov/pubmed/24939094

Meat Science • April 2015

The functionality of plum ingredients in meat products: a review

Author information

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Abstract

"Dried plums (prunes) have been marketed to consumers for consumption directly from the package as a convenient snack and have been reported to have broad health benefits. Only recently have fractionated, dried plum ingredients been investigated for their functionality in food and feed products. Dried plum puree, dried plum fiber, dried plum powder, dried plum concentrate, and fresh plum concentrate have been investigated to date. They have been evaluated as fat replacers in baked goods, antioxidants in meat formulations, phosphate replacers in chicken marinades, and antimicrobials in food systems. Overall, dried plum products have been shown to be effective at reducing lipid oxidation and show promise as antimicrobials."

http://www.ncbi.nlm.nih.gov/pubmed/25529288

“Both juices protected against Aß-induced cytotoxicity and apoptotic cell death ...”

Oxides In Medicine And Cellular Longevity • June 2015

Neuroprotective Effect of Brassica oleracea Sprouts Crude Juice in a Cellular Model of Alzheimer’s Disease

Author information

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Abstract

ß-Amyloid peptide (Aß) aberrant production and aggregation are major factors implicated in the pathogenesis of Alzheimer’s disease (AD), causing neuronal death via oxidative stress. Several studies have highlighted the importance of polyphenolic antioxidant compounds in the treatment of AD, but complex food matrices, characterized by a different relative content of these phytochemicals, have been neglected. In the present study, we analyzed the protective effect on SH-SY5Y cells treated with the fragment Aß 25-35 by two crude juices of broccoli sprouts containing different amounts of phenolic compounds as a result of different growth conditions. Both juices protected against Aß-induced cytotoxicity and apoptotic cell death as evidenced by cell viability, nuclear chromatin condensation, and apoptotic body formation measurements. These effects were mediated by the modulation of the mitochondrial function and of the HSP70 gene transcription and expression. Furthermore, the juices upregulated the intracellular glutathione content and mRNA levels or activity of antioxidant enzymes such as heme oxygenase-1, thioredoxin, thioredoxin reductase, and NAD(P)H: quinone oxidoreductase 1 via activation of NF-E2-related factor 2 (Nrf2). Although the effects of the two juices were similar, the juice enriched in phenolic compounds showed a greater efficacy in inducing the activation of the Nrf2 signalling pathway.

Full text, graphs, charts and 69 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4477226/

Microbiology Spectrum • June 2015

The Roles of Inflammation, Nutrient Availability and the Commensal Microbiota in Enteric Pathogen Infection

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Abstract

The healthy human intestine is colonized by as many as 1014 bacteria belonging to more than 500 different species forming a microbial ecosystem of unsurpassed diversity, termed the microbiota. The microbiota's various bacterial members engage in a physiological network of cooperation and competition within several layers of complexity. Within the last 10 years, technological progress in the field of next-generation sequencing technologies has tremendously advanced our understanding of the wide variety of physiological and pathological processes that are influenced by the commensal microbiota. An increasing number of human disease conditions, such as inflammatory bowel diseases (IBD), type 2 diabetes, obesity, allergies and colorectal cancer are linked with altered microbiota composition. Moreover, a clearer picture is emerging of the composition of the human microbiota in healthy individuals, its variability over time and between different persons and how the microbiota is shaped by environmental factors (i.e., diet) and the host's genetic background. A general feature of a normal, healthy gut microbiota can generate conditions in the gut that disfavor colonization of enteric pathogens. This is termed colonization-resistance (CR). Upon disturbance of the microbiota, CR can be transiently disrupted, and pathogens can gain the opportunity to grow to high levels. This disruption can be caused by exposure to antibiotics, changes in diet, application of probiotics and drugs, and a variety of diseases. Breakdown of CR can boost colonization by intrinsic pathogens or increase susceptibility to infections. One consequence of pathogen expansion is the triggering of inflammatory host responses and pathogen-mediated disease. Interestingly, human enteric pathogens are part of a small group of bacterial families that belong to the Proteobacteria: the Enterobacteriaceae (E. coli, Yersinia spp., Salmonella spp., Shigella spp.), the Vibrionaceae (Vibrio cholerae) and the Campylobacteriaceae (Campylobacter spp.). In general, members of these families (be it commensals or pathogens) only constitute a minority of the intestinal microbiota. However, proteobacterial "blooms" are a characteristic trait of an abnormal microbiota such as in the course of antibiotic therapy, dietary changes or inflammation (11). It has become clear that the gut microbiota not only plays a major role in priming and regulating mucosal and systemic immunity, but that the immune system also contributes to host control over microbiota composition. These two ways of mutual communication between the microbiota and the immune system were coined as "outside-in" and "inside-out," respectively (12). The significance of those interactions for human health is particularly evident in Crohn's disease (CD) and Ulcerative Colitis (UC). The symptoms of these recurrent, chronic types of gut inflammation are caused by an excessive immune response against one's own commensal microbiota (13). It is assumed that deregulated immune responses can be caused by a genetic predisposition, leading to, for example, the impairment of intestinal barrier function or disruption of mucosal T-cell homeostasis. In CD or UC patients, an abnormally composed microbiota, referred to as "dysbiosis," is commonly observed (discussed later). This is often characterized by an increased relative abundance of facultative anaerobic bacteria (e.g., Enterobacteriaeceae, Bacilli) and, at the same time, depletion of obligate anaerobic bacteria of the classes Bacteroidia and Clostridia. So far, it is unclear whether dysbiosis is a cause or a consequence of inflammatory bowel disease (IBD). In fact, both scenarios are equally conceivable. Recent work suggests that inflammatory immune responses in the gut (both IBD and pathogen-induced) can alter the gut luminal milieu in a way that favors dysbiosis (14). In this chapter, I present a survey on our current state of understanding of the characteristics and mechanisms underlying gut inflammation-associated dysbiosis. The role of dysbiosis in enteric infections and human IBD is discussed. In addition, I will focus on competition of enteric pathogens and the gut microbiota in the inflamed gut and the role of dysbiotic microbiota alterations (e.g., "Enterobacterial blooms" (11)) for the evolution of pathogenicity.

Full text with 181 references

http://www.asmscience.org/content/journal/microbiolspec/10.1128/microbiolspec.MBP-0008-2014#backarticlefulltext

“Epidemiological observations indicate that using alternative treatments, consumption of medicinal plants, diet, and consumption of fruits have had satisfactory results on the effects of hyperlipidemia in many societies. **It should be noted that in majority of societies, even developed countries, the tendency toward eating lipid-lowering medicinal plants has increased extensively.** Using these plants especially when common remedies cannot control the disease is significant.”

Journal Of Evidence Based Complementary Alternative Medicine • July 2015

A review on promising natural agents effective on hyperlipidemia

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Abstract

Hyperlipidemia is a prevalent disease and a major component of the metabolic syndrome resulting from various factors. This disease increases morbidity and mortality when combined with other prevalent diseases such as diabetes mellitus, hypertension, and cardiovascular diseases. The side effects of the current lipid-lowering drugs have increased the tendency to move toward traditional and alternative treatments. Epidemiological observations indicate that using alternative treatments, consumption of medicinal plants, diet, and consumption of fruits have had satisfactory results on the effects of hyperlipidemia in many societies. It should be noted that in majority of societies, even developed countries, the tendency toward eating lipid-lowering medicinal plants has increased extensively. Using these plants especially when common remedies cannot control the disease is significant. Although consumption of medicinal plants by hyperlipidemic patients may show improvement in disease state, drug interaction and side effects may cause complications in disease control. Therefore, in this review, apart from introducing some of the reliable plants effective in inhibition and decrease of hyperlipidemia, the possibility of their intoxication and drug interaction is also presented.

http://www.ncbi.nlm.nih.gov/pubmed/25633423

“The present results suggested that H. amblysepalum could be a potential candidate anti-cancer drug for the treatment of human cervical cancer, and good source of natural antioxidants.”

Asian Pacific Journal Of Cancer Prevention • July 2015

Antioxidant, anticancer and anticholinesterase activities of flower, fruit and seed extracts of Hypericum amblysepalum HOCHST

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Abstract

BACKGROUND

Cancer is an unnatural type of tissue growth in which the cells exhibit unrestrained division, leading to a progressive increase in the number of dividing cells. It is now the second largest cause of death in the world. The present study concerned antioxidant, anticancer and anticholinesterase activities and protocatechuic, catechin, caffeic acid, syringic acid, p-coumaric acid and o-coumaric concentrations in methanol extracts of flowers, fruits and seeds of Hypericum amblysepalum.

MATERIALS AND METHODS

Antioxidant properties including free radical scavenging activity and reducing power, and amounts of total phenolic compounds were evaluated using different tests. Protocatechuic, catechin, caffeic acid, syringic acid, p-coumaric acid and o-coumaric concentrations in extracts were determined by HPLC. Cytotoxic effects were determined using the MTT test with human cervix cancer (HeLa) and rat kidney epithelium cell (NRK-52E) lines. Acetyl and butyrylcholinesterase inhibitory activities were measured by by Ellman method.

RESULTS

Total phenolic content of H. amblysepalum seeds was found to be higher than in fruit and flower extracts. DPPH free radical scavenging activity of the obtained extracts gave satisfactory results versus butylated hydroxyanisole and butylated hydroxytoluene as controls. Reducing power activity was linearly proportional to the studied concentration range: 10-500 µg/ mL LC50 values for H. amblysepalum seeds were 11.7 and 2.86 respectively for HeLa and NRK-52E cell lines. Butyryl-cholinesterase inhibitory activity was 76.9±0.41 for seed extract and higher than with other extracts.

Full text PDF, graphs, charts and 44 references

http://www.apocpcontrol.org/paper_file/issue_abs/Volume16_No7/2763-2769%201.23%20Cumali%20Keskin.pdf

“Thus, lipid oxidation is prevented and shelf life is greatly enhanced by incorporating various kinds of fruits and their byproducts in meat and meat products. There is a great scope for the use of fruits as natural sources of antioxidants in meat industry.”

Critical Reviews In Food Science And Nutrition • July 2015

Fruit-based Natural Antioxidants in Meat and Meat Products: A Review

Author information

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Abstract

Due to the potential toxic effects of synthetic antioxidants, natural antioxidant sources especially fruits are being preferred now-a-days for use in different meat products. The majority of the antioxidant capacity of a fruit is especially because of numerous phenolic compounds. Many of the phytochemicals present in fruits may help protect cells against the oxidative damage caused by free radicals, thereby reducing the risk of degenerative diseases such as cardiovascular diseases, various types of cancers, and neurological diseases. Various parts of the fruit including their byproducts like skin and seeds have been used in meat products. Plum has been used as plum puree, prunes (dried plum), and plum extracts. Grape skin, seed, peel extracts, and grape pomace; berries as cakes and powder extracts; pomegranate rind powder and its juice; and most of the citrus fruits have proved beneficial sources of antioxidants. All these natural sources have effectively reduced the thiobarbituric acid-reactive substances (TBARS) values and free radical frequency. Thus, lipid oxidation is prevented and shelf life is greatly enhanced by incorporating various kinds of fruits and their byproducts in meat and meat products. There is a great scope for the use of fruits as natural sources of antioxidants in meat industry. The review is intended to provide an overview of the fruit-based natural antioxidants in meat and meat products.

http://www.ncbi.nlm.nih.gov/pubmed/24915314

“Meticulous processing with simple household practices like washing, dislodged the [pesticide] residues by 68 -72 per cent and thereby ensures the safety of the chilli fruits to the consumers.”

Journal of Food Processing & Technology • July 2015

Why Shoud We Wash All Fruits And Vegetables With Tap Water? Persistence and Effect of Processing on Reduction of Chlorpyriphos in Chilli

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Introduction

Pesticides help the farmers to increase their income by improving the quality of crop, saving crop losses, increase crop productivity and reduce cost of production. In recent years, the role and contribution of pesticides have increased much more, especially in the country like India because of fast growth of population; the demand for food supply will continue to grow steadily. Due to regular use of pesticides, the residues in food commodities seldom exceed the maximum residue limits (MRLs) set by the food authorities. As a result, consumption of pesticide treated food commodities become risky. So it becomes necessary that, pesticide should be effective against pest along with its toxicologically acceptable residues in food commodity [1]. For this reason, proper assessing of pesticide residues is very important for reducing health hazard to consumers. Chilli (Capsicum annum) is an essential pillar of the cuisines of India. It is attacked by various insect pests resulting in yield losses. The crop is attacked by various insect pests resulting 51 species of insects and 2 species of mites. Thrips, mites and pod borer are serious among its pests [2].

Chlorpyriphos [O,O-diethyl-O-(3,5,6-trichloro-2-pyridinyl) phosphorothionate] is an organo phosphorus broad spectrum insecticidal active ingredient registered for application to more than 40 different food commodities. It is a stable compound in neutral and acidic conditions [3]. It kills insects by disrupting their nervous system and is effective against both sucking and chewing insects and has been widely used to control pests of various vegetables [4]. It is non-systemic, fairly persistent, and highly soluble in organic solvents like acetone, xylene, and methylene chloride [5]. Cholinesterase inhibition is the mode of action of chlorpyriphos and is the cause of potential toxicity in human [6,7].

There is currently an increasing concern and awareness about the hazards of pesticides to consumers. Even with the adoption of integrated pest management, farmers believe in the control of pests using pesticides because of their quick effect. Therefore, the present study was designed to determine the residual persistence and effect of processing on reduction of chlorpyriphos residues in chilli.

Conclusion

From the above outcome, it is obvious that the application of pesticides in agriculture is necessary for better crop production against the possible health hazards arises due to the presence of pesticide residues in food. The half-life values for chlorpyriphos following three applications at the single and double dose on chilli fruits were observed to be 6.02 and 5.67 days, respectively. The residues of chlorpyriphos studied in chilli at two doses, reached to below detectable value of 0.01 mg kg-1 on 15th and 30th in single and double dose, respectively. Meticulous processing with simple household practices like washing, dislodged the residues by 68 -72 per cent and thereby ensures the safety of the chilli fruits to the consumers.

Full text, graphs, charts and 14 references

http://www.omicsonline.org/open-access/persistence-and-effect-of-processing-on-reduction-of-chlorpyriphos-in-chilli-2157-7110-1000497.pdf

“Gallic acid, caffeine and catechins were extracted within a very short period.
The maximum extractable polyphenols and flavanoids were achieved at 6-8 min after the tea brew is prepared.
Polyphenols, flavanoids and epigallocatechin gallate showed a significant correlation
with the antioxidant activity of tea.”

Nutrition Journal • July 2015

Extraction Kinetics of phytochemicals and antioxidant activity during black tea (Camellia sinensis L.) brewing

Fernando CD1,2, Soysa P3.

Abstract

BACKGROUND

Tea is the most consumed beverage in the world which is second only to water. Tea contains a broad spectrum of active ingredients which are responsible for its health benefits. The composition of constituents extracted to the tea brew depends on the method of preparation for its consumption. The objective of this study was to investigate the extraction kinetics of phenolic compounds, gallic acid, caffeine and catechins and the variation of antioxidant activity with time after tea brew is made.

METHODS

CTC (Crush, Tear, Curl) tea manufactured in Sri Lanka was used in this study. Tea brew was prepared according to the traditional method by adding boiling water to tea leaves. The samples were collected at different time intervals. Total phenolic and flavonoid contents were determined using Folin ciocalteu and aluminium chloride methods respectively. Gallic acid, caffeine, epicatechin, epigallocatechin gallate were quantified by HPLC/UV method. Antioxidant activity was evaluated by DPPH radical scavenging and Ferric Reducing Antioxidant Power (FRAP) assays.

RESULTS

Gallic acid, caffeine and catechins were extracted within a very short period. The maximum extractable polyphenols and flavanoids were achieved at 6-8 min after the tea brew is prepared. Polyphenols, flavanoids and epigallocatechin gallate showed a significant correlation ($p < 0.001$) with the antioxidant activity of tea.

Full text, graphs, charts and 35 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4520228/

“For this reason, olive leaf extracts warrant further investigation into their potential anti-pancreatic cancer benefits.”

Molecules • July 2015

Phytochemical properties and anti-proliferative activity of Olea europaea L. [Olive] leaf extracts against pancreatic cancer cells

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Abstract

Olea europaea L. leaves are an agricultural waste product with a high concentration of phenolic compounds; especially oleuropein. Oleuropein has been shown to exhibit anti-proliferative activity against a number of cancer types. However, they have not been tested against pancreatic cancer, the fifth leading cause of cancer related death in Western countries. Therefore, water, 50% ethanol and 50% methanol extracts of Corregiola and Frantoio variety Olea europaea L. leaves were investigated for their total phenolic compounds, total flavonoids and oleuropein content, antioxidant capacity and anti-proliferative activity against MiaPaCa-2 pancreatic cancer cells. The extracts only had slight differences in their phytochemical properties, and at 100 and 200 µg/mL, all decreased the viability of the pancreatic cancer cells relative to controls. At 50 µg/mL, the water extract from the Corregiola leaves exhibited the highest anti-proliferative activity with the effect possibly due to early eluting HPLC peaks. For this reason, olive leaf extracts warrant further investigation into their potential anti-pancreatic cancer benefits.

Full text, PDF, graphs, charts and 30 references

http://www.mdpi.com/1420-3049/20/7/12992

BMC Complementary Alternative Medicine • August 2015

Antioxidant potential, total phenolic and total flavonoid contents of Rhododendron anthopogonoides and its protective effect on hypoxia-induced injury in PC12 cells

Jing L1, Ma H1, Fan P1, Gao R1, Jia Z2.

Abstract

BACKGROUND

Rhododendron anthopogonoides Maxim, a kind of traditional Tibetan medicine, has been used to remove body heat, body detoxification, cough, asthma, stomachic and swelling, eliminate abundant phlegm and inflammatory for a long time. In the present study, the total phenols and total flavonoid contents as well as antioxidative properties of the crude extract and solvent fractions of R. anthopogonoides were determined using seven antioxidant assays. Additionally, the protective effect of the extracts on hypoxia-induced injury in PC12 cells was also investigated.

METHODS

The content of total flavonoid and total phenolic was determined by the aluminum colorimetric method and Folin-Ciocalteu assay, respectively. In vitro antioxidant study, the effect of the crude extract and solvent fractions on total antioxidant activity, reducing power, DPPH radical scavenging, ABTS radical scavenging, superoxide radical scavenging, hydroxyl radical scavenging and nitric oxide radical scavenging were examined. The correlation between the phenolic and flavonoid content of the extracts and their antioxidant properties also analyzed. Furthermore, the protective effect of extracts on hypoxia-induced damage on PC12 cells was investigated by cell viability, lactate dehydrogenase (LDH) release, malondialdehyde (MDA) production and the activities of antioxidant enzymes.

RESULTS

Our results showed that ethyl acetate and n-butanol fractions had higher content of phenolics and flavonoid compounds than other fractions. Except ABTS radical assay, n-butanol fraction exhibited the strongest antioxidant activity. While the hexane fraction showed the lowest antioxidant activity. Ethyl acetate also presented excellent antioxidant activity, which was just lower than n-butanol fraction. Significant correlation between the phenolic, flavonoid content of the extract and fractions with antioxidant assay excluding ABTS, OH scavenging assay was observed. Moreover, ethyl acetate and n-butanol fractions showed protective effect in PC12 cell under hypoxia condition, while crude extract and water fraction had no protective effect. In contrast, hexane fraction exhibited strong cytoprotective effect. Further study indicated that pretreatment of PC12 cells with ethyl acetate and n-butanol fractions, prior to hypoxia exposure, significantly increased the survival of cells and the activities of SOD, CAT, GSH-Px and T-AOC, as well as reduced the level of LDH and MDA. The gathered data demonstrated that ethyl acetate and n-butanol fractions were able to protect PC12 cells against hypoxia induced injury through direct free radical scavenging and modulation of endogenous antioxidant enzymes.

CONCLUSION

“These findings suggested that ethyl acetate and n-butanol fractions of R. anthopogonoides had significant antioxidant activity and could prevent PC12 cells against hypoxia-induced injury. So it might be regarded as an excellent source of antioxidants and had great potential to explore as therapeutic agent for preventing hypoxia related sickness in future.”

Full text, graphs, charts and 48 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4539926/

“The phytochemical analysis illustrated the presence of phenolic substances, mainly scopoletin, rutin, and chlorogenic acid, in these two active fractions. This study generates new information on the biological activity of L. domesticum.”

Nutrients • August 2015

Determination of Free Radical Scavenging, Antioxidative DNA Damage Activities and Phytochemical Components of Active Fractions from Lansium domesticum Corr. Fruit

Author information

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Abstract

Lansium domesticum Corr. or “long-kong” is one of the most popular fruits in Thailand. Its peel (skin, SK) and seeds (SD) become waste unless recycled or applied for use. This study was undertaken to determine the bioactivity and phytochemical components of L. domesticum (LD) skin and seed extracts. Following various extraction and fractionation procedures, 12 fractions were obtained. All fractions were tested for antioxidant capacity against O2(-•) and OH(•). It was found that the peel of L. domesticum fruits exhibited higher O2(-•) and OH(•) scavenging activity than seeds. High potential antioxidant activity was found in two fractions of 50% ethanol extract of peel followed by ethyl acetate (EA) fractionation (LDSK50-EA) and its aqueous phase (LDSK50-H2O). Therefore, these two active fractions were selected for further studies on their antioxidative activity against DNA damage by hydrogen peroxide (H2O2) in human TK6 cells using comet assay. The comet results revealed DNA-protective activity of both LDSK50-EA and LDSK50-H2O fractions when TK6 human lymphoblast cells were pre-treated at 25, 50, 100, and 200 µg/mL for 24 h prior to H2O2 exposure. The phytochemical analysis illustrated the presence of phenolic substances, mainly scopoletin, rutin, and chlorogenic acid, in these two active fractions. This study generates new information on the biological activity of L. domesticum. It will promote and strengthen the utilization of L. domesticum by-products.

Full text, graphs, charts and 49 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4555151/

Nutrition • September 2015

Durum Wheat Whole-meal Spaghetti with Tomato Peels: How By-product Particles Size Can Affect Final Quality of Pasta

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Conclusion

In this work, the impact of tomato peels-based flour addition on chemical composition, cooking and sensory quality of whole-meal durum wheat spaghetti was studied. In the first experimental step, tomato peels flour amount added to pasta dough was continuously increased until the sensory quality reached the threshold (tomato peels flour concentration 15%). In a second step, the influence of particles size on sensory quality of pasta with 15% tomato peels flour was investigated. The results indicated that the increase of particles size determined a decline of overall quality of samples; even a slight better nutritional composition was recorded. Specifically, the spaghetti enriched with the fine particles showed the greatest sensory score, due to the low fibrous, low adhesiveness, low bulkiness and high hardness values and showed a significant increase of starch digestibility. Therefore, our findings suggest that whole-meal spaghetti with fine particles represent fortified pasta with good sensory properties, very comparable to the control samples, and good cooking quality. This example of pasta fortification can offer a broad spectrum of new products with desired properties and encourage the use of agronomic by-products for further studies and new food applications.

Full text, graphs, charts and 26 references

http://www.omicsonline.org/open-access/durum-wheat-wholemeal-spaghetti-with-tomato-peels-how-byproduct-particles-size-can-affect-final-quality-of-pasta-2157-7110-1000500.pdf

Molecules • September 2015

Selected Phytochemicals and Culinary Plant Extracts Inhibit Fructose Uptake in Caco-2 Cells

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Abstract

This study compared the ability of nine culinary plant extracts containing a wide array of phytochemicals to inhibit fructose uptake and then explored the involvement of intestinal fructose transporters and phytochemicals for selected samples. The chemical signature was characterized by high performance liquid chromatography with mass spectrometry. Inhibition of [(14)C]-fructose uptake was tested by using human intestinal Caco-2 cells. Then, the relative contribution of the two apical-facing intestinal fructose transporters, GLUT2 and GLUT5, and the signature components for fructose uptake inhibition was confirmed in naive, phloretin-treated and forskolin-treated Caco-2 cells. HPLC/MS analysis of the chemical signature revealed that guava leaf contained quercetin and catechin, and turmeric contained curcumin, bisdemethoxycurcumin and dimethoxycurcumin. Similar inhibition of fructose uptake (by ~50%) was observed with guava leaf and turmeric in Caco-2 cells, but with a higher contribution of GLUT2 for turmeric and that of GLUT5 for guava leaf. The data suggested that, in turmeric, demethoxycurcumin specifically contributed to GLUT2-mediated fructose uptake inhibition, and curcumin did the same to GLUT5-mediated fructose uptake inhibition, but GLUT2 inhibition was more potent. By contrast, in guava leaf, catechin specifically contributed to GLUT5-mediated fructose uptake inhibition, and quercetin affected both GLUT5- and GLUT2-mediated fructose uptake inhibition, resulting in the higher contribution of GLUT5. These results suggest that demethoxycurcumin is an important contributor to GLUT2-mediated fructose uptake inhibition for turmeric extract, and catechin is the same to GLUT5-mediated fructose uptake inhibition for guava leaf extract. Quercetin, curcumin and bisdemethoxycurcumin contributed to both GLUT5- and GLUT2-mediated fructose uptake inhibition, but the contribution to GLUT5 inhibition was higher than the contribution to GLUT2 inhibition.

Full text, link to PDF, graphs, charts and 22 references

http://www.mdpi.com/1420-3049/20/9/17393

“The results also show that avocado fruit extract has profound influence on leptin activity, which controls satiety and hunger to regulate the food intake.”

Phytomedicine • September 2015

The modulating effect of Persea americana fruit extract on the level of expression of fatty acid synthase complex, lipoprotein lipase, fibroblast growth factor-21 and leptin-- A biochemical study in rats subjected to experimental hyperlipidemia and obesity

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Abstract

BACKGROUND

Obesity is a multifactorial disorder which is closely associated with hyperlipidemia. Avocados are edible fruits traditionally consumed for various health benefits including body weight reduction.

HYPOTHESIS/PURPOSE

To determine the hypolipidemic and anti-obesity effect of hydro-alcoholic fruit extract of avocado (HFEA) in rats fed with high fat diet (HFD).

STUDY DESIGN

Male Sprague Dawley rats were divided into four groups. Groups 1 and 2 rats were fed with normal diet. Groups 3 and 4 rats were fed with HFD for 14 weeks. In addition, Groups 2 and 4 rats were co-administered with 100 mg/kg body weight of HFEA from 3rd week onwards.

METHODS

The HFEA was subjected to HPLC to quantify the major phytonutrients. Body mass index (BMI), adiposity index (ADI), total fat pad mass (TFP), blood lipid levels were determined in all the groups of rats. The mRNA expression of fatty acid synthase (FASN), lipoprotein lipase (LPL), fibroblast growth factor 21 (FGF21) and leptin was also assessed.

RESULTS

HFEA was found to contain flavonoids: rutin-141.79, quercetin-5.25, luteolin-165, phenolic compounds: gallic acid-198.57, ellagic acid-238.22, vanillic acid-4.79 and phytosterols: betasitosterol-70, stigmasterol-12.5 (mg/100 g). HFEA reduced BMI, ADI, TFP, blood cholesterol, triglycerides, and LDL in rats fed with HFD. Serum leptin was found reduced in HFEA co-administered rats. The mRNA expression of FASN, LPL, and leptin in subcutaneous and visceral adipose tissue was found to be significantly reduced in HFEA co-administered rats. The gene expression of fibroblast growth factor-21 (FGF21) was found to be significantly increased in HFEA treated rats when compared to HFD control rats.

CONCLUSION

The hypolipidemic effect of HFEA may be partly due to its modulating effect on endogenous fat synthesis and adiponectin formation through the transcription factor FGF21. The results also show that avocado fruit extract has profound influence on leptin activity, which controls satiety and hunger to regulate the food intake.

http://www.ncbi.nlm.nih.gov/pubmed/26321743

“The essential oil showed stronger antioxidant potential in comparison with synthetic antioxidants (i.e., BHA and BHT) in a rapeseed oil model system. The oil exhibited also stronger radical scavenging activity against DPPH·radical in comparison with synthetic antioxidants. The diversity of applications to which Nigella sativa essential oil can be put gives this oil industrial importance.”

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Health-promoting value and food applications of black cumin essential oil: an overview

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Abstract

Black cumin (Nigella sativa L.) seeds and its essential oil have been widely used in functional foods, nutraceuticals and pharmaceutical products. Analysis of Nigella sativa essential oil using GC and GC-MS resulted in the identification of many bioactive compounds representing ca. 85 % of the total content. The main compounds included p-cymene, thymoquinone, ß-thujene, longifolene, ß-pinene, a-pinene and carvacrol. Nigella sativa essential oil exhibited different biological activities including antifungal, antibacterial and antioxidant potentials. Nigella sativa essential oil showed complete inhibition zones against different Gram-negative and Gram-positive bacteria including Penicillium citrinum Bacillus cereus, Bacillus subtilis, Staphylococcus aureus and Pseudomonas aeruginosa. The essential oil showed stronger antioxidant potential in comparison with synthetic antioxidants (i.e., BHA and BHT) in a rapeseed oil model system. The oil exhibited also stronger radical scavenging activity against DPPH·radical in comparison with synthetic antioxidants. The diversity of applications to which Nigella sativa essential oil can be put gives this oil industrial importance.

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Alpha-amylase Inhibition and Antioxidant Activity of Marine Green Algae and its Possible Role in Diabetes Management

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Abstract

AIM

In the continuing search for safe and efficient antidiabetic drug, marine algae become important source which provide several compounds of immense therapeutic potential. Alpha-amylase, alpha-glucosidase inhibitors, and antioxidant compounds are known to manage diabetes and have received much attention recently. In the present study, four green algae (Chaetomorpha aerea, Enteromorpha intestinalis, Chlorodesmis, and Cladophora rupestris) were chosen to evaluate alpha-amylase, alpha-glucosidase inhibitory, and antioxidant activity in vitro.

MATERIALS AND METHODS

The phytochemical constituents of all the extracts were qualitatively determined. Antidiabetic activity was evaluated by inhibitory potential of extracts against alpha-amylase and alpha-glucosidase by spectrophotometric assays. Antioxidant activity was determined by 2,2-diphenyl-1-picrylhydrazyl, hydrogen peroxide (H2O2), and nitric oxide scavenging assay. Gas chromatography-mass spectrometry (GC-MS) analysis was carried out to determine the major compound responsible for its antidiabetic action.

RESULTS

Among the various extracts screened, chloroform extract of C. aerea (IC50 - 408.9 µg/ml) and methanol extract of Chlorodesmis (IC50 - 147.6 µg/ml) showed effective inhibition against alpha-amylase. The extracts were also evaluated for alpha-glucosidase inhibition, and no observed activity was found. Methanol extract of C. rupestris showed notable free radical scavenging activity (IC50 - 666.3 µg/ml), followed by H2O2 (34%) and nitric oxide (49%). Further, chemical profiling by GC-MS revealed the presence of major bioactive compounds. Phenol, 2,4-bis (1,1-dimethylethyl) and z, z-6,28-heptatriactontadien-2-one were predominantly found in the methanol extract of C. rupestris and chloroform extract of C. aerea.

CONCLUSION

Our results demonstrate that the selected algae exhibit notable alpha-amylase inhibition and antioxidant activity. Therefore, characterization of active compounds and its in vivo assays will be noteworthy.

SUMMARY

Four green algae were chosen to evaluate alpha-amylase, alpha-glucosidase inhibitory, and antioxidant activity in vitro C. aerea and Chlorodesmis showed significant inhibition against alpha-amylase, and C. rupestris showed notable free radical scavenging activity. No observed activity was found against alpha-glucosidaseGC-MS analysis of the active extracts reveals the presence of major compounds which gives an insight on the antidiabetic and antioxidant activity of these algae. Abbreviations used: DPPH: 2,2-diphenyl-1-picrylhydrazyl, BHT: Butylated hydroxytoluene, GC-MS: Gas chromatography-mass spectrometry.

Full text, graphs, charts and 17 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4787081/

“Milling is the critical process affecting the concentrations of nutrients in wheat-derived food products. The outer parts of the kernel, especially the aleurone layer and the germ are richer in minerals. Conventional milling reduces nutritional content in flour and concentrates them in the milling residues.”

Nutrition • October 2015

Effect of Refined Milling on the Nutritional Value and Antioxidant Capacity of Wheat Types Common in Ethiopia and a Recovery Attempt with Bran Supplementation in Bread

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Introduction

Wheat has accompanied humans since remote times (as far back as 3000 to 4000 BC) in their evolution and development, evolving itself (in part by nature and in part by manipulation) from its primitive form (emmer wheat) into the presently cultivated species [1]. Wheat crop is widely adapted to a variety of environments and is cultivated in tropical, subtropical and temperate areas [2]. It is widely consumed by humans, in the countries of primary production (which number over 100 in the FAO production statistics for 2004) and in other countries where wheat cannot be grown [3]. It also occupies 27 percent of the total cereal production worldwide [1]. It is thus, an important agricultural commodity which is consumed in large amount all over the world among all grains.

Ethiopia is the largest wheat producer in sub-Saharan Africa [4]. Nationally, wheat ranks fourth in total area coverage (1,389, 215.00 ha). It is also third in productivity (after maize and sorghum) among cereals [5]. It is one of the most important crops grown and consumed in Ethiopia both in terms of total production (2.85 million MT in 2010/11) [6] and the proportion of total calories consumed in the country (19.6% of calories consumed) [7].

Wheat possesses several health benefits, especially when utilized as a wholegrain product. According to Kumar [8], wheat provides protection against diseases such as constipation, ischaemic, heart disease, diverticulum, appendicitis, diabetes and obesity. These benefits are attributed in part to the presence of different compounds such as dietary fibers, phytochemicals, proteins, vitamins and minerals [9].

Whole wheat grain consists of bran, germ and endosperm. When refined, only carbohydrate rich endosperm is retained. This results in a big loss of many nutritionally valuable biochemical compounds such as dietary fiber, vitamins, minerals and antioxidant compounds which play an important role in reducing cardiovascular disease (CVD) [10]. When white flour is produced, many important nutrients and fibre are removed, because these components are mainly located in bran and germ [11]. Wheat bran is rich in protein (~14%), carbohydrates (~27%), minerals (~5%) and fat (~6%) [12]. In addition, bran is the main by-product produced by milling. Wheat bran is a most important fiber source which is inexpensive and available. It is a good source of not only dietary fiber but also for other major nutrients. The loss of vitamins and minerals in the refined wheat flour has led to widespread prevalence of constipation and other digestive disturbances and nutritional disorders [8].

Milling is the critical process affecting the concentrations of nutrients in wheat-derived food products. The outer parts of the kernel, especially the aleurone layer and the germ are richer in minerals. Conventional milling reduces nutritional content in flour and concentrates them in the milling residues [13]. White flour with the extraction rate 68% meaning up to 32% of the original grain is not in the flour. Whole grain flour includes all parts of the seed and is 100% extraction. Milling of wheat into highly refined flours not only preclude considerable amounts of nutrients from human consumption, but the remaining flours have a much poorer nutritive value than flour made from whole wheat.
Over the past twenty years, wheat production and consumption have both increased in Ethiopia [14]. On top of this wheat flour covers a substantial proportion of the population. According to the survey conducted in Ethiopia, 28% of consumers purchase flour and flour products. It is estimated that wheat flour reaches about 22 million people [15]. However, no published information is available regarding the effect of refining on nutritional and antioxidant capacity of wheat that are commonly grown in Ethiopia though it is widely distributed and consumed. The nutritional value and antioxidant properties of wheat grain are significantly influenced by soil type and richness, growing temperatures, moisture levels, other climatic differences, and genotype [16].

It is therefore, very important to understand the nutritional value of wheat grown in Ethiopia and evaluate after the effect of refined milling. In addition, it is necessary to find a way to improve the nutrient quality of the refined wheat flour products without compromising the palatability of the product. Hence, in this study an attempt was also made to recover the nutrients through supplementation of bran in wheat bread making.

Full text, graphs, charts, photos and 40 references

http://www.omicsonline.org/open-access/effect-of-refined-milling-on-the-nutritional-value-and-antioxidantcapacity-of-wheat-types-common-in-ethiopia-and-a-recovery-attemptwith-bran-supplementation-in-bread-2157-7110-1000506.pdf

Nutrition • October 2015

Comparison of Ascorbic Acid, Total Phenolic Content and Antioxidant Activities of Fresh Juices of Six Fruits Grown in Oman

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Introduction

Oxidative stress is believed to be involved in causation of more than hundred chronic diseases such as cancer, diabetes, cardiovascular and degenerative diseases etc. [1]. One of the possible ways to fight these diseases is to reinforce our body's antioxidant defense system. Antioxidants possess the ability to scavenge the free radicals and protect the body from damages caused by the oxidative stress [2]. In order to strengthen our immunity and to maintain good health, we must supply our body with the natural antioxidants present in exogenous sources such as vegetables, fruits, cereals, grains, beverages and hot drinks etc through the balanced diet [3].

Fruits are important part of a healthy diet and are rich in vitamins, fibres, minerals, micro nutrients and phenolic compounds [4]. Fruits have very high antioxidant value in comparison to vegetables and cereals [5]. Therefore, regular consumption of fruits and their juices play a beneficial role in the prevention and progression of many chronic diseases owing to the presence of dietary antioxidants such as ascorbic acid, flavonoids and polyphenols [6-8]. Fruits are also routinely consumed as fresh juices due to their suitability for ingestion which supply a relevant part of intake of health promoting polyphenolic phytochemicals [9].

Fruits and vegetables constitute the important part of Omani diet. Fruits are the fourth largest source of food nutrition and in quantitative terms it is more than the average daily consumption of Fish and meat together in Oman [10]. Fruits such as lime, lemon, grapefruit (citrus), melons (water and sweet) and pomegranate are the local commercial agricultural produce of Oman. Citrus fruits are known for their high ascorbic acid content, a natural antioxidant that protects the organism from oxidative stress [11] but in addition to ascorbate, there are other phytochemicals present such as phenolics and anthocyanins that contribute more to the antioxidant capacity than ascorbate [12].

The present study was undertaken to determine and compare total phenolics, ascorbic acid content and to investigate free radical scavenging activity of six ripe fruits namely Citrus aurantifolia, Citrus paradise, Citrus limon, Cucumis melo, Citrullus lanatus and Punica granatum locally grown and commonly consumed fruits in Oman.

Conclusion

The juices upon quantification by colorimetric method were found to be rich in phenolic compounds (tannins and flavonoids) and therefore exhibited very good free radical scavenging activity. Based on the results, it can be concluded that these fruit juices could be used as a natural source of antioxidants and their regular consumption could provide health benefits to humans by shielding against oxidative stress.

Full text, graphs, charts and 22 references

http://www.omicsonline.org/open-access/comparison-of-ascorbic-acid-total-phenolic-content-and-antioxidant-activities-of-fresh-juices-of-six-fruits-grown-in-oman-2157-7110-1000513.pdf

Critical Reviews In Food Science And Nutrition • November 2015

Benzoic Acid and Its Derivatives as Naturally Occurring Compounds in Foods and as Additives: Uses, Exposure and Controversy

Author information

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Abstract

“Benzoic acid is an aromatic carboxylic acid naturally present in plant and animal tissues which can also be produced by microorganisms. Benzoic acid and a wide range of derivatives and related benzenic compounds, such as salts, alkyl esters, parabens, benzyl alcohol, benzaldehyde and benzoyl peroxide, are commonly used as antibacterial and antifungal preservatives and as flavouring agents in food, cosmetic, hygiene, and pharmaceutical products. As the result of their widespread occurrence, production and uses, these compounds are largely distributed in the environment being found in water, soil, and air. Consequently, human exposure to them can be high, common and lengthy. This review is mainly focused on the presence and use of benzoic acid in foods but it also covers the occurrence, uses, human exposure, metabolism, toxicology, analytical methods for detection and legal limits for benzoic acid and its derivatives. Their controversial effects and potential public health concerns are discussed.”

http://www.ncbi.nlm.nih.gov/pubmed/26587821

Biomedical And Environmental Science • November 2015

Cancer Therapy with Phytochemicals: Present and Future Perspectives

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Abstract

“Recently, a wide range of food-derived phytochemical compounds and their synthetic derivatives have been proposed for cancer treatment. Unfortunately, data available in related literature focus on the anti-cancer properties of compounds derived from edible plants, while very little is known about those derived from non-edible plants. And thus, the underlying mechanisms of their anti-cancer effects are yet to be elucidated. This review collates the available data on the anti-cancer activities of six phytochemical-derived compounds from edible and non-edible plants, i.e. rottlerin, berbamine, sparstolonin B, sulforaphane, plumbagin and 6-shogaol. These compounds are used as bioactive markers for cytotoxicity against tumors. As such, understanding their mode of action will provide the rationale for the combination strategies of these compounds with other drugs in the battle against cancer.”

http://www.ncbi.nlm.nih.gov/pubmed/26695359

“The results of the study indicate that Cucumber green mottle mosaic virus infection significantly changes the physiology of cucumbers, affecting the expression levels of individual proteins as well as entire metabolic pathways.”

Virology Journal• December.2015

Quantitative proteomics identifies 38 proteins that are differentially expressed in cucumber in response to cucumber green mottle mosaic virus infection

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Abstract

BACKGROUND

Since it was first reported in 1935, Cucumber green mottle mosaic virus (CGMMV) has become a serious pathogen in a range of cucurbit crops. The virus is generally transmitted by propagation materials, and to date no effective chemical or cultural methods of control have been developed to combat its spread. The current study presents a preliminary analysis of the pathogenic mechanisms from the perspective of protein expression levels in an infected cucumber host, with the objective of elucidating the infection process and potential strategies to reduce both the economic and yield losses associated with CGMMV.

METHODS

Isobaric tags for relative and absolute quantitation (iTRAQ) technology coupled with liquid chromatography-tandem mass spectrometric (LC-MS/MS) were used to identify the differentially expressed proteins in cucumber plants infected with CGMMV compared with mock-inoculated plants. The functions of the proteins were deduced by functional annotation and their involvement in metabolic processes explored by KEGG pathway analysis to identify their interactions during CGMMV infection, while their in vivo expression was further verified by qPCR.

RESULTS

Infection by CGMMV altered both the expression level and absolute quantity of 38 proteins (fold change >0.6) in cucumber hosts. Of these, 23 were found to be up-regulated, while 15 were down-regulated. Gene ontology (GO) analysis revealed that 22 of the proteins had a combined function and were associated with molecular function (MF), biological process (BP) and cellular component (CC). Several other proteins had a dual function with 1, 7, and 2 proteins being associated with BP/CC, BP/MF, CC/MF, respectively. The remaining 3 proteins were only involved in MF. In addition, Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis identified 18 proteins that were involved in 13 separate metabolic pathways. These pathways were subsequently merged to generate three network diagrams illustrating the interactions between the different pathways, while qPCR was used to track the changes in expression levels of the proteins identified at 3 time points during CGMMV infection. Taken together these results greatly expand our understanding of the relationships between CGMMV and cucumber hosts.

CONCLUSIONS

The results of the study indicate that CGMMV infection significantly changes the physiology of cucumbers, affecting the expression levels of individual proteins as well as entire metabolic pathways. The bioinformatic analysis also identified several pathogenesis-related (PR) proteins that could be useful in the development of disease-resistant plants.

Full text, graphs, charts and 79 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4678648/

“Amla (Indian gooseberry) and its processed products are rich source of vitamin C, phenols, dietary fibre and antioxidants. In contrast, ice cream is a poor source of these phytochemicals and antioxidants; therefore, the present investigation was undertaken to enhance the functional properties and nutritional quality of ice cream with the incorporation of processed amla. The functional constituents i.e. fibre, total phenols, tannins, ascorbic acid and antioxidant activity increased with greater level of inclusion.”

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Enhancing the functional properties and nutritional quality of ice cream with processed amla (Indian gooseberry)

Author information

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Abstract

Amla (Indian gooseberry) and its processed products are rich source of vitamin C, phenols, dietary fibre and antioxidants. In contrast, ice cream is a poor source of these phytochemicals and antioxidants; therefore, the present investigation was undertaken to enhance the functional properties and nutritional quality of ice cream with the incorporation of processed amla. Ice cream was prepared using amla shreds, pulp, preserve and candy at 5 to 20 % and powder at 0.5 to 2.0 % levels in ice cream mix prior to freezing. Inclusion of amla products at augmented levels resulted in significant changes in physico-chemical properties and phytochemical content of ice cream. The total solids decreased on addition of shreds and pulp and increased with preserve, candy and powder in ice cream at increasing levels. The functional constituents i.e. fibre, total phenols, tannins, ascorbic acid and antioxidant activity increased with greater level of inclusion. Incorporation of processed amla raised the melting resistance of ice cream and decreased the overrun. The samples with 5 % shreds and pulp, 10 % preserve and candy and 0.5 % powder were found to have highest overall acceptability scores. Inclusion of amla in all the forms i.e. shreds, pulp, preserve, candy and powder enhanced the functional properties and nutritional value of ice cream.

http://www.ncbi.nlm.nih.gov/pubmed/26604358

“A variety of activities such as bactericidal, membrane-penetrating, antimicrobial, anti-hypertensive, pro-angiogenic and others have been reported for arginine-rich proteins.”

Current Protein And Peptide Science • December 2015

Occurrence, Functions and Biological Significance of Arginine-Rich Proteins

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Abstract

Arginine, the most basic among the 20 amino acids, occurs less frequently than lysine in proteins despite being coded by six codons. Only a few important proteins of biological significance have been found to be abundant in arginine. It has been established that these arginine-rich proteins have been assigned important roles in the biological systems. Arginine-rich cationic proteins are known to stabilize macromolecular structures by establishing appropriate interactions (salt bridges, hydrogen bonds and cation-π interactions). These proteins are also known to be the key members of many regulatory pathways such as gene expression, chromatin stability, expurgation of introns from naïve mRNA, mRNA splicing, membrane-penetrating activity and pathogenesis-related defense, to name a few. Further, arginine occurs in various combinations with other amino acids (serine, lysine, proline, tryptophan, valine, glycine and glutamic acid) which diversify the potential functions of arginine-rich proteins. Arginine-rich proteins known till date from dietary sources have been described in terms of their structure and functional properties. A variety of activities such as bactericidal, membrane-penetrating, antimicrobial, anti-hypertensive, pro-angiogenic and others have been reported for arginine-rich proteins. This review attempts to collate the occurrence, functions and the biological significance of this unique class of proteins rich in arginine.

http://www.ncbi.nlm.nih.gov/pubmed/26916156

“Some nutraceuticals, when adequately dosed, should improve a number of the Metabolic Syndrome components.”

Phytomedicine • December 2015

Role of phytochemicals in the management of metabolic syndrome

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Abstract

BACKGROUND

The World Health Organization (WHO) for some years has been focusing on what is now commonly referred to as an “epidemic of obesity and diabetes” (“diabesity”): behind this outbreak, there are several risk factors grouped in what is called “metabolic syndrome” (MetS). The basis of this “epidemic” is either a diet too often characterized by excessive consumption of saturated and trans-esterified fatty acids, simple sugars and salt, either a sedentary lifestyle.

PURPOSE

The aim of this review is to focus on the phytochemicals that have a more positive effect on the treatment and/or prevention of MetS.

CHAPTERS

Treatment strategies for MetS include pharmacologic and non-pharmacologic options, with varying degrees of success rate. The first is indicated for patients with high cardiovascular risk, while the second one is the most cost-effective preventive approach for subjects with borderline parameters and for patients intolerant to pharmacological therapy. MetS non-pharmacological treatments could involve the use of nutraceuticals, most of which has plant origins (phytochemicals), associated with lifestyle improvement. The chapter will discuss the available evidence on soluble fibres from psyllium and other sources, cinnamaldehyde, cinnamic acid and other cinnamon phytochemicals, berberine, corosolic acid from banaba, charantin from bitter gourd, catechins and flavonols from green tea and cocoa. Vegetable omega-3 polyunsaturated fatty acids, alliin from garlic, soy peptides, and curcumin from curcuma longa.

CONCLUSION

Some nutraceuticals, when adequately dosed, should improve a number of the MetS components.

http://www.ncbi.nlm.nih.gov/pubmed/26778479

“The prevalence of obesity has steadily increased over the past three decades both in the United States and worldwide. Recent studies have shown the role of dietary polyphenols in the prevention of obesity and obesity-related chronic diseases.”

Journal Of Nutritional Biochemistry • January 2014

Novel insights of dietary polyphenols and obesity

Author information
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Abstract

The prevalence of obesity has steadily increased over the past three decades both in the United States and worldwide. Recent studies have shown the role of dietary polyphenols in the prevention of obesity and obesity-related chronic diseases. Here, we evaluated the impact of commonly consumed polyphenols, including green tea catechins, especially epigallocatechin gallates, resveratrol and curcumin, on obesity and obesity-related inflammation. Cellular studies demonstrated that these dietary polyphenols reduce viability of adipocytes and proliferation of preadipocytes, suppress adipocyte differentiation and triglyceride accumulation, stimulate lipolysis and fatty acid k-oxidation, and reduce inflammation. Concomitantly, the polyphenols modulate signaling pathways including the adenosine-monophosphate-activated protein kinase, peroxisome proliferator activated receptor k, CCAAT/enhancer binding protein k, peroxisome proliferator activator receptor gamma activator 1-alpha, sirtuin 1, sterol regulatory element binding protein-1c, uncoupling proteins 1 and 2, and nuclear factor-kB that regulate adipogenesis, antioxidant and anti-inflammatory responses. Animal studies strongly suggest that commonly consumed polyphenols described in this review have a pronounced effect on obesity as shown by lower body weight, fat mass and triglycerides through enhancing energy expenditure and fat utilization, and modulating glucose hemostasis. Limited human studies have been conducted in this area and are inconsistent about the antiobesity impact of dietary polyphenols probably due to the various study designs and lengths, variation among subjects (age, gender, ethnicity), chemical forms of the dietary polyphenols used and confounding factors such as other weight-reducing agents. Future randomized controlled trials are warranted to reconcile the discrepancies between preclinical efficacies and inconclusive clinic outcomes of these polyphenols.

Full text, graphs, charts and 179 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3926750/

“Its main constituents subsume coumarins, furanocoumarins (bergapten, imperatori), ascorbic acid, carotenoids, flavonoids, apiole, various terpenoic compounds, phenyl propanoids, phathalides, and tocopherol. Due to these constituents, it has been annunciated to possess a number of possible medicinal emblematics including, antimicrobial, antianemic, menorrhagic, anticoagulant, antihyperlipidemic, antihepatotoxic, antihypertensive, diuretic effects, hypoglycaemic, hypouricemic, anti oxidative and estrogenic activities. In Morocco, Parsley is mostly used as an elixir to treat arterial hypertension, diabetes, cardiac and renal diseases. Antioxidant and antibacterial activities of parsley, made it propitious in food systems.”

Pakistan Journal Of Pharmaceutical Science • January 2014

Critique of medicinal conspicuousness of Parsley (Petroselinum crispum): a culinary herb of Mediterranean region

Author information

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Abstract

WHO estimates, around 80% of the especially developing world is indigent on complementary and alternative medicines which are prodigiously derived from herbal material. Parsley (Petroselinum crispum) is an important culinary herb originated from the Mediterranean region. It possesses small and dark seeds with volatile oil content. Petroselinum crispum is now planted throughout the world due to its usage in food industry, perfume manufacturing, soaps, and creams. Its main constituents subsume coumarins, furanocoumarins (bergapten, imperatori), ascorbic acid, carotenoids, flavonoids, apiole, various terpenoic compounds, phenyl propanoids, phathalides, and tocopherol. Due to these constituents, it has been annunciated to possess a number of possible medicinal emblematics including, antimicrobial, antianemic, menorrhagic, anticoagulant, antihyperlipidemic, antihepatotoxic, antihypertensive, diuretic effects, hypoglycaemic, hypouricemic, anti oxidative and estrogenic activities. In Morocco, Parsley is mostly used as an elixir to treat arterial hypertension, diabetes, cardiac and renal diseases. Antioxidant and antibacterial activities of parsley, made it propitious in food systems. Its ELI17 gene has been corroborated as a particularly fast-responding gene. There is a requisite for extensive research to avail the maximal benefits of this significant medicinal plant. The aim of this review paper is to divulge the chemical constituents of parsley that are explicitly related to substantial medicinal facets.

http://www.ncbi.nlm.nih.gov/pubmed/24374449

Trends in Food Science & Technology • February 2014

Functional foods against metabolic syndrome (obesity, diabetes, hypertension and dyslipidemia) and cardiovasular disease

Author Information
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Highlights

- The article reviews the current knowledge of functional foods to fight cardiovascular disease
- The foods that help manage obesity or dyslipidemia and modes of action.
- The various foods that help manage diabetes and mechanisms of action.
- The various foods that help manage hypertension and mechanisms of action.

“Metabolic syndrome is a condition of at least three of the cardiovascular risk factors: obesity, excessive visceral fat storage, dyslipidemia, hypertension and hyperglycaemia or Type 2 diabetes. It is a state of insulin resistance, oxidative stress and chronic inflammation. Cardiovascular disease is the highest cause of death globally. Certain dietary components and over 800 plants help prevent or moderate metabolic syndrome by assisting the body homeostasis mechanisms. This review compiles the most current studies on foods that help fight metabolic syndrome and the scientific evidences to support their use. This includes functional fats, digestive enzymes inhibitors, various beverages, different fruits, specific vegetables, grains, legumes, herbs and spices that can reduce cardiovascular disease risk, through several cellular mechanisms.”

Full text, PDF, graphs, charts and 156 references

http://www.silae.it/files/FST_Functional%20Food.pdf

“ ...this prooxidant chemopreventive mechanism
appears to be a mechanism common to several polyphenols with diverse chemical structures
and explains the preferential cytotoxicity of these compounds toward cancer cells.”

Molecular And Nutritional Food Research • March 2014

Plant polyphenol induced cell death in human cancer cells involves mobilization of intracellular copper ions and reactive oxygenspecies generation: a mechanism for cancer chemopreventive action

Author information

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Farhan M, Sarkar FH, Ahmad A, Hadi SM.

Department of Biochemistry, Faculty of Life Sciences, AMU, Aligarh, India

Abstract

SCOPE

Anticancer polyphenolic nutraceuticals from fruits, vegetables, and spices are generally recognized as antioxidants, but can be prooxidants in the presence of copper ions. We earlier proposed a mechanism for such activity of polyphenols and now we provide data in multiple cancer cell lines in support of our hypothesis.

METHODS AND RESULTS

Through multiple assays, we show that polyphenols luteolin, apigenin, epigallocatechin-3-gallate, and resveratrol are able to inhibit cell proliferation and induce apoptosis in different cancer cell lines. Such cell death is prevented to a significant extent by cuprous chelator neocuproine and reactive oxygen species scavengers. We also show that normal breast epithelial cells, cultured in a medium supplemented with copper, become sensitized to polyphenol-induced growth inhibition.

CONCLUSION

Since the concentration of copper is significantly elevated in cancer cells, our results strengthen the idea that an important anticancer mechanism of plant polyphenols is mediated through intracellular copper mobilization and reactive oxygen species generation leading to cancer cell death. Moreover, this prooxidant chemopreventive mechanism appears to be a mechanism common to several polyphenols with diverse chemical structures and explains the preferential cytotoxicity of these compounds toward cancer cells.

http://www.ncbi.nlm.nih.gov/pubmed/24123728

“[P]attern recognition receptor complexes are under tight control by protein phosphatases, E3 ligases, and other regulatory proteins, illustrating the exquisite and complex regulation of these molecular machines whose proper activation underlines a crucial layer of plant immunity.”

Molecules And Cells • April 2014

Plant PRRs and the activation of innate immune signaling

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Abstract

Despite being sessile organisms constantly exposed to potential pathogens and pests, plants are surprisingly resilient to infections. Plants can detect invaders via the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs). Plant PRRs are surface-localized receptor-like kinases, which comprise a ligand-binding ectodomain and an intracellular kinase domain, or receptor-like proteins, which do not exhibit any known intracellular signaling domain. In this review, we summarize recent discoveries that shed light on the molecular mechanisms underlying ligand perception and subsequent activation of plant PRRs. Notably, plant PRRs appear as central components of multiprotein complexes at the plasma membrane that contain additional transmembrane and cytosolic kinases required for the initiation and specificity of immune signaling. PRR complexes are under tight control by protein phosphatases, E3 ligases, and other regulatory proteins, illustrating the exquisite and complex regulation of these molecular machines whose proper activation underlines a crucial layer of plant immunity.

Full text, graphs, charts and 98 references

http://www.cell.com/molecular-cell/abstract/S1097-2765(14)00261-5

“This study adds to the growing body of data supporting the bioactivities of phytochemicals and their potential impact on human health.”

Anticancer Agents In Medicinal Chemistry • July 2014

Antioxidant activity and chemical components as potential anticancer agents in the olive leaf (Olea europaea L. cv Leccino.) decoction

Author information

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Abstract

Epidemiological studies have shown that a reduced risk of chronic diseases such as cancer and cardiovascular diseases is correlated with a regular consumption of fruits and vegetable, many of which are rich in polyphenols. The additive and synergistic effect of phytochemicals in fruits and vegetables may reduce chronic diseases related to oxidative stress in human body. Olea europaea L. leaf are rich in phenolic components, which have been proposed to play a role in cancer prevention. The purpose of this study was to identify the main components in the Olea europaea L. leaf (cv. Leccino) preserved during the decoction preparation, in order to delineate the antioxidant activities of the crude extracts and its isolated compounds by using different in vitro assays including DPPH radicalscavenging capacity, total antioxidant capacity (TAC), xanthine oxidase (XO) inhibitory effect and the ability to delay the linoleic acid peroxidation process (ALP). The aqueous decoction was partitioned obtaining four extracts and the n-butanol extract showed the highest antioxidant activity and the highest total phenolic content. Phytochemical investigation leads to the isolation of thirteen secondary metabolites including simple phenolics, flavonoids, secoiridoids whose structures were elucidated by spectroscopic data (1D and 2D NMR) and spectrometric techniques. A significant free radical scavenging effect against DPPH has been evidenced in fraxamoside (1) (EC50 62.6 μM) and taxifolin (5) (EC50 50.0 μM), isolated for the first time from the water decoction. The most active compound in the TAC evaluation, was the 3,4 dihydro-phenyl glycol (8) (0.90 caffeic acid equiv.) while taxifolin and fraxamoside resulted as the most efficient inhibitors of XO activity (IC50 2.7 and 5.2 μM, respectively). Secoxyloganin (4), oleuropein (2) and tyrosol (6) showed the highest ALP activity. This study adds to the growing body of data supporting the bioactivities of phytochemicals and their potential impact on human health.

http://www.ncbi.nlm.nih.gov/pubmed/25102361

PLoS One • August 2014

Anti-inflammatory activity of Odina wodier Roxb, an Indian folk remedy, through inhibition of toll-like receptor 4 signaling pathway

Author information
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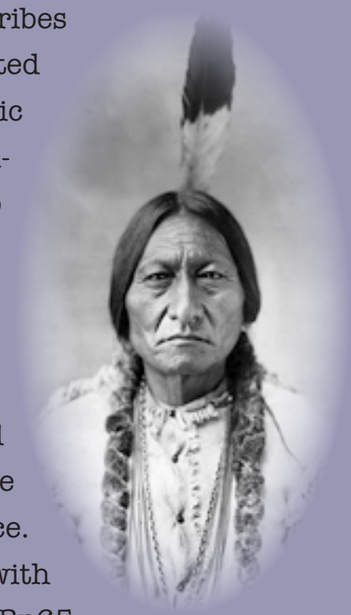
Mondal KC3, Malhotra B4, Samanta A5, Chattopadhyay D2.

Abstract

“Inflammation is part of self-limiting non-specific immune response, which occurs during bodily injury. In some disorders the inflammatory process becomes continuous, leading to the development of chronic inflammatory diseases including cardiovascular diseases, diabetes, cancer etc. Several Indian tribes used the bark of Odina wodier (OWB) for treating inflammatory disorders. Thus, we have evaluated the immunotherapeutic potential of OWB methanol extract and its major constituent chlorogenic acid (CA), using three popular in vivo antiinflammatory models: Carrageenan- and Dextran-induced paw edema, Cotton pellet granuloma, and Acetic acid-induced vascular permeability. To elucidate the possible anti-inflammatory mechanism of action we determine the level of major inflammatory mediators (NO, iNOS, COX-2-dependent prostaglandin E2 or PGE2), and pro-inflammatory cytokines (TNF-ß, IL-1ß, IL-6, and IL-12). Further, we determine the toll-like receptor 4 (TLR4), Myeloid differentiation primary response gene 88 (MyD88), c-Jun N-terminal kinases (JNK), nuclear factor kappa-B cells (NF-ßB), and NF-kB inhibitor alpha (IK-Bß) by protein and mRNA expression, and Western blot analysis in drug treated LPS-induced murine macrophage model. Moreover, we determined the acute and sub-acute toxicity of OWB extract in BALB/c mice. Our study demonstrated a significant anti-inflammatory activity of OWB extract and CA along with the inhibition of TNF-ß, IL-1ß, IL-6 and IL-12 expressions. Further, the expression of TLR4, NF-ßBp65, MyD88, iNOS and COX-2 molecules were reduced in drug-treated groups, but not in the LPS-stimulated untreated or control groups, Thus, our results collectively indicated that the OWB extract and CA can efficiently inhibit inflammation through the down regulation of TLR4/MyD88/NF-kB signaling pathway.”



Full text, graphs, charts and 47 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4143220/pdf/pone.0104939.pdf

Current Psychiatry Reports • August 2014

Natural products and supplements for geriatric depression and cognitive disorders: an evaluation of the research

Author information

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Abstract

“Numerous geriatric patients are using Complementary and Alternative Medicine (CAM) for late-life mood and cognitive disorders. Natural products and supplements are a common CAM intervention which have risks and benefits of which patients should be appropriately advised. The data for omega-3 fatty acids, ginkgo biloba, SAMe, St John’s wort, B vitamins and vitamin D, huperzine, caprylidene, and coconut oil will be evaluated. Since the evidence basis for natural products and supplements is limited, especially for the geriatric population, studies involving the general adult population are included to infer effects in the aging population. Despite the data available, more rigorous studies with larger sample sizes over longer periods of time are still needed. Regardless of a physician’s preference to recommend various natural supplements and products, a physician could protect their patients by having an understanding of the side effects and indications for various natural products.”

Full text with 87 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110105/

“Grape seed, green tea, pine bark, rosemary, pomegranate, nettle and cinnamon have exhibited similar or better antioxidant properties compared to some synthetic ones.”

Meat Science • September 2014

Plant extracts as natural antioxidants in meat and meat products

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Abstract

Antioxidants are used to minimize the oxidative changes in meat and meat products. Oxidative changes may have negative effects on the quality of meat and meat products, causing changes in their sensory and nutritional properties. Although synthetic antioxidants have already been used but in recent years, the demand for natural antioxidants has been increased mainly because of adverse effects of synthetic antioxidants. Thus most of the recent investigations have been directed towards the identification of natural antioxidants from various plant sources. Plant extracts have been prepared using different solvents and extraction methods. Grape seed, green tea, pine bark, rosemary, pomegranate, nettle and cinnamon have exhibited similar or better antioxidant properties compared to some synthetic ones. This review provides the recent information on plant extracts used as natural antioxidants in meat and meat products, specifically red meat.

http://www.ncbi.nlm.nih.gov/pubmed/24824531

Iranian Journal On Basic Medical Science • December 2014

Black cumin (Nigella sativa) and its constituent (thymoquinone): a review on antimicrobial effects

Author information

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3. Pharmaceutical Research Center, Pharmacodynamy and Toxicology Department, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

“Nigella sativa seeds have wide therapeutic effects and have been reported to have significant effects against many ailments such as skin diseases, jaundice, gastrointestinal problems, anorexia, conjunctivitis, dyspepsia, rheumatism, diabetes, hypertension, intrinsic hemorrhage, paralysis, amenorrhea, anorexia, asthma, cough, bronchitis, headache, fever, influenza and eczema. Thymoquinone (TQ) is one of the most active constituent and has different beneficial properties. Focus on antimicrobial effects, different extracts of N. sativa as well as TQ, have a broad antimicrobial spectrum including Gram-negative, Gram-positive bacteria, viruses, parasites, schistosoma and fungi. The effectiveness of N. sativa seeds and TQ is variable and depends on species of target microorganisms. The present review paper tries to describe all antimicrobial activities that have been carried out by various researchers.”

Full text, graphs, charts and 71 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4387228/

“To the best of our knowledge, this study provides the first evidence that kolaviron could act as an acetylcholinesterase inhibitor. Kolaviron may be developed as a herbal-based natural product with therapeutic potential in the management of neurodegenerative disorders associated with disturbed cholinergic neurotransmitter systems.”

Annals In Neuroscience • April 2013

Kolaviron, isolated from Garcinia kola, inhibits acetylcholinesterase activities in the hippocampus and striatum of wistar rats

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2. Department of Human Anatomy,, Cross River University of Technology, Okuku, Cross River
3. Department of Anatomy and Neurobiology, Imo State University, Owerri, Imo, Nigeria

Abstract

Background
Kolaviron, isolated from seeds of Garcinia kola, have been shown to possess wide pharmacological properties.
Purpose
The present study examined the effect of kolaviron on acetylcholinesterase activities in the hippocampus and striatum of adult Wistar rats.
Methods
In this study, histological and histochemical methods were used to investigate the effects of kolaviron on the histology of the hippocampus and striatum and on acetylcholinesterase activities in these brain regions.
Results
We showed that kolaviron produced no neurodegenerative changes in the hippocampus and striatum. Kolaviron did not significantly alter ($p<0.05$) neuronal density in these brain regions. Kolaviron significantly reduced ($p<0.05$) acetylcholinesterase staining intensity, suggesting a likely inhibiting effect on this enzyme.
Conclusion
To the best of our knowledge, this study provides the first evidence that kolaviron could act as an acetylcholinesterase inhibitor. Kolaviron may be developed as a herbal-based natural product with therapeutic potential in the management of neurodegenerative disorders associated with disturbed cholinergic neurotransmitter systems.

Full text, graphs, charts and 24 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4117109/pdf/ANS0972-7531-20-042.pdf

“Kolaviron may be developed as a herbal-based natural product with therapeutic potential in the management of neurodegenerative disorders associated with disturbed cholinergic neurotransmitter systems.”

Annals In Neuroscience • April 2013

Kolaviron, isolated from Garcinia kola, inhibits acetylcholinesterase activities in the hippocampus and striatum of wistar rats

Author Information
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Abstract

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We showed that kolaviron produced no neurodegenerative changes in the hippocampus and striatum. Kolaviron did not significantly alter ($p<0.05$) neuronal density in these brain regions. Kolaviron significantly reduced ($p<0.05$) acetylcholinesterase staining intensity, suggesting a likely inhibiting effect on this enzyme.
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To the best of our knowledge, this study provides the first evidence that kolaviron could act as an acetylcholinesterase inhibitor. Kolaviron may be developed as a herbal-based natural product with therapeutic potential in the management of neurodegenerative disorders associated with disturbed cholinergic neurotransmitter systems.

Full text, graphs, charts and 24 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4117109/pdf/ANS0972-7531-20-042.pdf

“Potatoes, in all forms, when consumed in MyPlate serving sizes, can be part of health-promoting dietary patterns.”

Advances In Nutrition • May 2013

White vegetables: a forgotten source of nutrients: Purdue roundtable executive summary

Author information

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Abstract

Purdue University convened a scientific roundtable, “White Vegetables: A Forgotten Source of Nutrients,” in Chicago, IL, June 18-19, 2012, to bring together experts to address the contributions of white vegetables, including potatoes, as sources of key nutrients and other microconstituents within a dietary pattern supporting health and wellness. This paper summarizes the meeting and supplement papers, including discussion among participants. The group of researchers identified areas of ambiguity regarding classification of vegetables for research and dietary guidance, future research needs, and the imperative to draw on that research to enhance evidence-based dietary guidance about white vegetables, including potatoes. U.S. dietary guidance encourages consumption of a variety of fruits and vegetables, including at least 1 serving of a dark green and 1 orange vegetable daily. However, no such recommendation exists for white vegetables, such as potatoes, cauliflowers, turnips, onions, parsnips, mushrooms, corn, and kohlrabi. Vegetable subgrouping approaches need to be considered in the context of nutrients of concern and low fruits and vegetable consumption. This Roundtable and supplement provide a substantial body of evidence to demonstrate how the inclusion of white vegetables, such as potatoes, can increase shortfall nutrients, notably fiber, potassium, and magnesium, as well as help increase overall vegetable consumption among children, teens, and adults in the United States. In so doing, these increases can help consumers to effectively and economically meet the recommended 2010 Dietary Guidelines for Americans vegetable servings and improve nutrient intake for all age and sex categories. Although inclusion of many types of vegetables in the diet improves nutritional adequacy, a priority public health message is to increase vegetable consumption. Potatoes appear to be a pathway to increased vegetable consumption, thereby helping to meet the recommended 2010 Dietary Guidelines for Americans servings for vegetables provided the forms served limit the amount of added salt and fat. Potatoes, in all forms, when consumed in MyPlate serving sizes, can be part of health-promoting dietary patterns. More research is needed to determine the health contributions of white vegetables as a source of nutrients and bioactive constituents and their bioavailability beyond the isolated components.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23674800

Advances In Nutrition • May 2013

Contributions of white vegetables to nutrient intake: NHANES 2009-2010

Author information

Storey ML1, Anderson PA.

Abstract

“Vegetables, especially white potatoes, provide significant levels of key nutrients of concern, such as potassium and dietary fiber. Per capita availability (PCA) data for vegetables-often used as a proxy for vegetable consumption-show that vegetable consumption, including consumption of white potatoes, declined in the past decade. Using dietary data for participants in the NHANES 2009-2010, we examined total vegetable, white potato, and French-fried potato consumption among all age-gender groups as well as mean energy, potassium, and dietary fiber intakes. Mean total energy intake for the US population (≥2 y old) was 2080 kcal/d, with white potatoes and French-fried potatoes providing ~4% and ~2% of total energy, respectively. Individuals who consumed white potatoes had significantly higher total vegetable and potassium intakes than did nonconsumers. In addition, the proportion of potassium and dietary fiber contributed by white potatoes was higher than the proportion that they contributed to total energy. Among white potato consumers aged 14-18 y, white potatoes provided ~23% of dietary fiber and ~20% of potassium but only ~11% of total energy in the diet. The nutrient-dense white potato may be an effective way to increase total vegetable consumption and potassium and dietary fiber intake.”

Full text, graphs, charts and 28 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3650505/

“Regular consumption of fruits, vegetables, whole grains, and other plant foods has been negatively correlated with the risk of the development of chronic diseases. There is a huge gap between the average consumption of fruits and vegetables in Americans and the amount recommended by the 2010 Dietary Guidelines for Americans. Therefore, consumers should obtain their nutrients, antioxidants, bioactive compounds, and phytochemicals from a balanced diet with a wide variety of fruits, vegetables, whole grains, and other plant foods for optimal nutrition, health, and well-being, not from dietary supplements.”

Advances In Nutrition • May 2013

Health-promoting components of fruits and vegetables in the diet

Author information

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Abstract

Regular consumption of fruits, vegetables, whole grains, and other plant foods has been negatively correlated with the risk of the development of chronic diseases. There is a huge gap between the average consumption of fruits and vegetables in Americans and the amount recommended by the 2010 Dietary Guidelines for Americans. The key is to encourage consumers to increase the total amount to 9 to 13 servings of fruits and vegetables in all forms available. Fresh, processed fruits and vegetables including frozen and canned, cooked, 100% fruit juices and 100% vegetable juices, as well as dry fruits are all considered as servings of fruits and vegetables per day. A wide variety of fruits, vegetables, whole grains, and other plant foods provide a range of nutrients and different bioactive compounds including phytochemicals, vitamins, minerals, and fibers. Potatoes serve as one of the low-fat foods with unique nutrients and phytochemical profiles, particularly rich in vitamin C, vitamin B-6, potassium, manganese, and dietary fibers. Potatoes provide 25% of vegetable phenolics in the American diet, the largest contributors among the 27 vegetables commonly consumed in the United States, including flavonoids (quercetin and kaempferol), phenolic acids (chlorogenic acid and caffeic acid), and carotenoids (lutein and zeaxanthin). More and more evidence suggests that the health benefits of fruits, vegetables, whole grains, and other plant foods are attributed to the synergy or interactions of bioactive compounds and other nutrients in whole foods. Therefore, consumers should obtain their nutrients, antioxidants, bioactive compounds, and phytochemicals from a balanced diet with a wide variety of fruits, vegetables, whole grains, and other plant foods for optimal nutrition, health, and well-being, not from dietary supplements.

Full text with 68 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3650511/

Meat Science • June 2013

Natural antioxidants in meat and poultry products

Author information

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Abstract

“In response to recent claims that synthetic antioxidants have the potential to cause toxicological effects and consumers’ increased interest in purchasing natural products, the meat and poultry industry has been seeking sources of natural antioxidants. Due to their high phenolic compound content, fruits and other plant materials provide a good alternative to conventional antioxidants. Plum, grape seed extract, cranberry, pomegranate, bearberry, pine bark extract, rosemary, oregano, and other spices functions as antioxidants in meat and poultry products. Pomegranate, pine bark extract, cinnamon, and cloves have exhibited stronger antioxidant properties than some synthetic options. Plum products, grape seed extract, pine bark extract, rosemary, and some spices all have been shown to affect the color of finished meat or poultry products; however, in some products such as pork sausage or uncured meats, an increase in red color may be desired. When selecting a natural antioxidant, sensory and quality impact on the product should be considered to achieve desired traits.”

http://www.ncbi.nlm.nih.gov/pubmed/23501254

“Flavonoids are the most numerous group of natural polyphenolic compounds, the secondary metabolites of plants that may play an important role in human health protection. Flavonols and flavones constitute the main two classes of flavonoids, whose antioxidant properties and high biological activity have been proofed both in vitro and in vivo.”

Voprosy Pitaniia • July 2013

Biologically active substances of plant origin
Flavonols and flavones: prevalence, dietary sourses and consumption

Tutel’ian VA, Lashneva NV.

Abstract

Flavonoids are the most numerous group of natural polyphenolic compounds, the secondary metabolites of plants that may play an important role in human health protection. Flavonols and flavones constitute the main two classes of flavonoids, whose antioxidant properties and high biological activity have been proofed both in vitro and in vivo. This review summarizes data, concerning the structure, occurrence and content of the main flavonols (quercetin, kaempherol, myricetin, isorhamnetin) and flavones (apigenin, luteolin) in some most widely consumed foodstuffs, including vegetables, fruits, berries, nuts, beverages and other products of plant origin. The products with high content of these biologically active food compounds--the major dietary sources of them--are noted. Forms of flavonols and flavones more often distributed among edible plants are characterized and some of their known glycosides occurred in foods are enumerated. Some peculiarities, characteristic to flavonol sand flavones glycosilation (O- and/or C-glycosides formation) are described. The data for flavonol and flavone glycosides composition (profiles) of some commonly consumed commodities rich by these flavonoids (onions, cabbage, apples at al.) are shown. Information about levels of daily dietary intake of total and individual flavonols and flavones in several countries is presented. The questions about dietary habits and lifestyle factors and the contribution of certain foods to flavonols and flavones in daily dietary consumption values are also discussed.

http://www.ncbi.nlm.nih.gov/pubmed/23808274

“These Thai indigenous fruits are potentially good sources of nutrients, bioactive compounds, and antioxidant activities. Conservation and utilisation should be promoted for food security and consumption as part of a healthy diet.”

Food Chemistry • October 2013

Nutrients and bioactive compounds of Thai indigenous fruits

Author information

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Abstract

This study determined the nutritional potential of Thai indigenous fruits in terms of nutrients, bioactive compounds, and antioxidant activities. Three indigenous fruits were collected at two conservation areas in Kanchanaburi province, Thailand. The results showed that Phyllanthus emblica L. exhibited the highest levels of vitamin C (575±452mg/100g), total phenolics (TP) (3703±1244mGAE/100g), and antioxidant activities, as measured by DPPH, FRAP and ORAC assays. Compared to the other two fruits, Antidesma velutinosum Blume contained higher levels of most nutrients and dietary fibre (15.6±5.9g/100g), as well as carotenoids (335±98µg/100g) and phytosterols (22.1±3.9mg/100g). Spondias pinnata (L.f.) Kurz was high in total phenolics (3178±887mGAE/100g) and antioxidant activity. Moreover, high correlations were found between TP and antioxidant activities (r>0.9). These Thai indigenous fruits are potentially good sources of nutrients, bioactive compounds, and antioxidant activities. Conservation and utilisation should be promoted for food security and consumption as part of a healthy diet.

http://www.ncbi.nlm.nih.gov/pubmed/23601399

“Whole wheat flour and bread were superior to refined flour and bread in in vitro antioxidant properties.”

Antioxidants (Basel) • November 2013

Comparison of Antioxidant Properties of Refined and Whole Wheat Flour and Bread

Author information

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Abstract

Antioxidant properties of refined and whole wheat flour and their resultant bread were investigated to document the effects of baking. Total phenolic content (TPC), 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity and oxygen radical absorbance capacity (ORAC) were employed to determine the content of ethanol extractable phenolic compounds. HPLC was used to detect the presence of phenolic acids prior to their confirmation using LC-MS/MS. Whole wheat flour showed significantly higher antioxidant activity than refined flour ($p < 0.05$). There was a significant effect of the bread-making process with the TPC of whole wheat bread (1.50-1.65 mg/g) and white bread (0.79-1.03 mg/g) showing a respective reduction of 28% and 33% of the levels found in whole wheat and refined flour. Similarly, baking decreased DPPH radical scavenging capacity by 32% and 30%. ORAC values, however, indicated that baking increased the antioxidant activities of whole wheat and refined flour by 1.8 and 2.9 times, respectively. HPLC analysis showed an increase of 18% to 35% in ferulic acid after baking to obtain whole and refined wheat bread containing 330.1 and 25.3 µg/g (average), respectively. Whole wheat flour and bread were superior to refined flour and bread in in vitro antioxidant properties.

Full text, graphs, charts and 40 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4665520/

“The traditional use of Odina wodier bark for the management of skin infections has scientific basis.”

Journal Of Applied Microbiology • December 2013

Evaluation of anti-infective potential of a tribal folklore Odina wodier Roxb against some selected microbes and herpes simplex virus associated with skin infection

Author information

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CMR Virus Unit, I.D. & B.G. Hospital, Beliaghata, Kolkata, India

Abstract

AIM: To evaluate the in vitro antimicrobial activity of aqueous and methanol extracts of Odina wodier bark (OWB), a folk medicine, against representative bacteria, fungi and herpes simplex virus (HSV) associated with skin infections.

METHODS AND RESULTS

The OWB extract(s) was found to inhibit the isolates of Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli at an MIC of 256-5000 µg ml(-1) and Candida albicans at and above 4000 µg ml(-1) by agar and broth dilution assays. The growth curve of Staph. aureus revealed the highest activity within 2-6 h of methanol extract (ME) exposure. Interestingly, the MTT and plaque reduction assay showed that the extracts can inhibit HSV-1 and HSV-2 at EC50 of 22·4 and 28·8 µg ml(-1) , with Selectivity index of 11·7-15. While the time kinetic and binding assays demonstrated that the ME at 50 µg ml(-1) prevents viral attachment into Vero cells. Phytochemical and HPLC analysis of ME revealed the presence of flavonoids, phytosterols, saponins and tannins including the pseudotannin chlorogenic acid.

CONCLUSION

The traditional use of OWB for the management of skin infections has scientific basis.

SIGNIFICANCE AND IMPACT OF THE STUDY

This study demonstrated the antimicrobial potential of OWB on selected isolates of bacteria, fungi and HSV, associated with skin infections.

http://www.ncbi.nlm.nih.gov/pubmed/23957446

“It is expectant that this study resulted in improvement the tendencies toward Petroselinum crispum as a useful and important medicinal plant with wide range of proven medicinal activity.”

The Journal Of Traditional Chinese Medicine • December 2013

Parsley:
a review of ethnopharmacology, phytochemistry and biological activities

Farzaei MH, Abbasabadi Z, Ardekani MR, Rahimi R, Farzaei F.

Abstract

OBJECTIVE:
To summarize comprehensive information concerning ethnomedicinal uses, phytochemistry, and pharmacological activities of parsley.

METHODS:
Databases including PubMed, Scopus, Google Scholar, and Web of Science were searched for studies focusing on the ethnomedicinal use, phytochemical compounds and biological and pharmacological activities of parsley. Data were collected from 1966 to 2013. The search terms were: “Parsley” or “Petroselinum crispum” or “Petroselinum hortence”.

RESULTS:
Parsley has been used as carminative, gastro tonic, diuretic, antiseptic of urinary tract, anti-urolithiasis, anti-dote and anti-inflammatory and for the treatment of amenorrhea, dysmenorrhea, gastrointestinal disorder, hypertension, cardiac disease, urinary disease, otitis, sniffle, diabetes and also various dermal disease in traditional and folklore medicines. Phenolic compounds and flavonoids particularly apigenin, apiin and 6”-Acetylapiin; essential oil mainly myristicin and apiol; and also coumarins are the active compounds identified in Petroselinum crispum. Wide range of pharmacological activity including antioxidant, hepatoprotective, brain protective, anti-diabetic, analgesic, spasmolytic, immunosuppressant, anti-platelet, gastroprotective, cytoprotective, laxative, estrogenic, diuretic, hypotensive, antibacterial and antifungal activities have been exhibited for this plant in modern medicine.

CONCLUSION:
It is expectant that this study resulted in improvement the tendencies toward Petroselinum crispum as a useful and important medicinal plant with wide range of proven medicinal activity.

Full text, PDF, graphs, charts and 19 references

http://www.journaltcm.com/modules/Journal/contents/stories/136/3.pdf

Journal of Functional Foods • January 2012

Crucial facts about health benefits of popular cruciferous vegetables

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Abstract

"The lower incidences of many chronic diseases such as cancer and cardiovascular related ailments are associated with consumption of vegetables rich dietary regimes and this has been substantiated through numerous in vitro, pre-clinical and clinical investigations. Members of cruciferous family are cultivated and widely consumed universally as a part of daily diet. The major vegetables includes broccoli, cauliflower, radish, kale, brussels sprouts, watercress and cabbage that are used either fresh (salads), steamed or cooked. Besides nutritional components, these vegetables are also rich in health beneficial secondary metabolites, which include sulfur containing glucosinolates and S-methylcysteine sulfoxide, flavonoids, anthocyanins, coumarins, carotenoids, antioxidant enzymes, terpenes and other minor compounds. Based on the worldwide popularity and health benefits of these vegetables, this review provides collective information on nutritional and health benefits. In addition, information on evidence based therapeutic and prophylactic benefits of commonly used cruciferous vegetables are discussed with emphasis on cancer and cardiovascular disease. Some of the unique mechanisms of cancer inhibition such as effect on Nrf2, polymorphism, anti-inflammatory, inhibition of histone deacetylase activity and influence on estrogen metabolism are also included."

http://www.sciencedirect.com/science/article/pii/S1756464611000843

“In this review, we will briefly discuss causes of oxidative stress in Alzheimer’s disease brains, and describe antioxidant neuroprotective effects and therapeutic potential for Alzheimer’s disease of selected natural polyphenolic compounds.”

Brain Research Bulletin • February 2012

Antioxidant properties of natural polyphenols and their therapeutic potentials for Alzheimer’s disease

Author information

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Abstract

Alzheimer’s disease (AD) is the most prevalent neurodegenerative disease and most common cause of dementia. However, there is no known way to halt or cure the neurodegenerative disease. Oxidative stress is a cardinal hallmark of the disease and has been considered as therapeutic target for AD treatment. Several factors may contribute to oxidative stress in AD brains. First, mitochondrion is a key player that produces reactive oxygen species (ROS). Mitochondrial dysfunction found in AD patients may exaggerate generation of ROS and oxidative stress. Second, amyloid-beta peptide generates ROS in the presence of metal ions such as Fe(2+) and Cu(2+). Third, activated glial cells in AD brains may produce excessive amount of superoxide and nitric oxide through NADPH oxidase and inducible nitric oxide synthase, respectively. Increased ROS can cause damage to protein, lipid and nucleic acids. Numerous studies demonstrated that natural polyphenolic compounds protect against various neurotoxic insults in vitro and in vivo AD models. In these studies, dietary polyphenolic compounds exhibit neuroprotective effects through scavenging free radicals and increasing antioxidant capacity. Furthermore, they could facilitate the endogenous antioxidant system by stimulating transcription. Some epidemiological and clinical studies highlighted their therapeutic potential for AD treatment. In this review, we will briefly discuss causes of oxidative stress in AD brains, and describe antioxidant neuroprotective effects and therapeutic potential for AD of selected natural polyphenolic compounds.

http://www.ncbi.nlm.nih.gov/pubmed/22155297

“These results corroborate the increasing importance of polyphenols as human dietary supplements in amelioration of the cognitive impairment during aging and neurological disorders such as Alzheimer’s Disease.”

Behavior And Brain Research • March 2012

LMN diet, rich in polyphenols and polyunsaturated fatty acids, improves mouse cognitive decline associated with aging and Alzheimer’s disease

Author information

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Abstract

We examined whether LMN diet, reported to induce neurogenesis in adult mice, was able to antagonize the age-related behavioural impairment and neuropathology in wild type (WT) mice and Tg2576 mice, a mouse model of Alzheimer’s disease (AD). Thirteen-month-old mice (once the amyloid (Aß) plaques were formed) were fed with the LMN diet for 5 months, and in the last 2 months of the regimen they received a battery of behavioural tests. In general, both aging and (to a higher extent) Tg2576 genotype deteriorated sensorimotor reflexes, exploratory behaviour in the hole board, activity (but not anxiety) in the elevated plus-maze, ambulation in the home cage during the dark phase, and spatial learning in the Morris water maze. LMN diet did not affect the detrimental effects observed in sensorimotor reflexes, but clearly reversed the effects of both aging and Tg2576 genotype. This behavioural amelioration was correlated with a 70% increase in cellular proliferation in subventricular zone (SVZ) of the brain, but did not correlate with a decrease of amyloid plaques. In contrast, administration of LMN diet to 10 months old mice (before the plaques are formed) strongly suggested a putative delay in the formation of plaques, as indicated by a decreasing tendency of soluble and fibrillar Aß levels in hippocampus which correlated with a decrease in Aß (1-40, 1-42) plasma content. Herein we describe for the first time that LMN diet rich in polyphenols, dry fruits and cocoa, was able to decrease behavioural deterioration caused by aging and Tg2576 genotype and to delay the Aß plaque formation. These results corroborate the increasing importance of polyphenols as human dietary supplements in amelioration of the cognitive impairment during aging and neurological disorders such as AD.

http://www.ncbi.nlm.nih.gov/pubmed/22119712

“This review discusses such a copper-dependent prooxidant mechanism of action of polyphenols that accounts for their observed chemopreventive properties, as also for their preferential cytotoxicity towards cancer cells.”

Current Drug Targets • December 2012

A prooxidant mechanism for the anticancer and chemopreventive properties of plant polyphenols

Author information

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Abstract

Plant-derived polyphenols, a prominent class of phytochemicals, are considered important components of human diet. A number of them are known to possess chemopreventive and therapeutic properties against various diseases including cancer. Several studies using cancer cell lines and animal models of carcinogenesis have shown that a wide range of polyphenols possess anticancer and apoptosis-inducing properties. Notably, an important aspect of the chemopreventive action of polyphenols is their differential activity in selectively targeting cancer cells while sparing normal cells. However, the mechanism through which polyphenols modulate their cancer cell selective anticancer effects has not been clearly delineated. In this regard, identification of a definitive anticancer mechanism of polyphenols would contribute to establish them as potent lead compounds for the synthesis of novel anticancer drugs. Although polyphenols are generally recognized as antioxidants, they also act as prooxidants inducing DNA degradation in the presence of metal ions such as copper. Based on our own observations and those of others, a mechanism for the anticancer properties of polyphenols that involves mobilization of chromatin-bound copper and consequent prooxidant action leading to cell death, was proposed. Since it is known that tissue and cellular copper levels are significantly elevated in a number of malignancies, cancer cells would be more subject to redox cycling between copper ions and polyphenols to generate reactive oxygen species (ROS) responsible for DNA breakage. This review discusses such a copper-dependent prooxidant mechanism of action of polyphenols that accounts for their observed chemopreventive properties, as also for their preferential cytotoxicity towards cancer cells.

http://www.ncbi.nlm.nih.gov/pubmed/23140285

“Thus, although nutritional supplements are at the peak of dietetic therapies, the consumption of some specific foods (legumes, fatty fish, vegetables and fruits, etc) with bioactive components within an energy-restricted diet is a promising approach to manage metabolic syndrome manifestations. Therefore, the present review focuses on some of the most important food components currently investigated to improve and make easier the nutritional metabolic syndrome treatment.”

Nutrition, Metabolism And Cardiovascular Disease • September 2011

Obesity and metabolic syndrome: potential benefit from specific nutritional components

Author information

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Abstract

The prevalence of metabolic syndrome (MetS) manifestations is rapidly increasing worldwide, and is becoming an important health problem. Actually, MetS includes a combination of clinical complications such as obesity (central adiposity), insulin resistance, glucose intolerance, dyslipidemia, non-alcoholic fatty liver disease and hypertension. All these alterations predispose individuals to type 2 diabetes and cardiovascular disease inducing earlier mortality rates among people. In general terms, it is difficult for patients to follow a standard long-term diet/exercise regime that would improve or alleviate MetS symptoms. Thus, the investigation of food components that may deal with the MetS features is an important field for ameliorate and facilitate MetS dietary-based therapies. Currently antioxidants are of great interest due to the described association between obesity, cardiovascular alterations and oxidative stress. On the other hand, high MUFA and PUFA diets are being also considered due to their potential benefits on hypertension, insulin resistance and triglyceride levels. Mineral composition of the diet is also relevant since high potassium intake may improve hypertension and high calcium consumption may promote lipid oxidation. Thus, although nutritional supplements are at the peak of dietetic therapies, the consumption of some specific foods (legumes, fatty fish, vegetables and fruits, etc) with bioactive components within an energy-restricted diet is a promising approach to manage MetS manifestations. Therefore, the present review focuses on some of the most important food components currently investigated to improve and make easier the nutritional MetS treatment.

http://www.ncbi.nlm.nih.gov/pubmed/21764273

“Taken together, understanding of immunologic cross-reactivity is essential to advance our knowledge about allergy. Additionally, this knowledge might help in the development of intelligent tools for the prediction of allergenicity of novel proteins or foods to which individuals previously have not been exposed. In fact, profilins, nsLTPs, and a Bet v 1 homologue were identified in vegetable varieties that were recently introduced to the European market.”

Allergy, Asthma And Clinical Immunology • January 2010

Panallergens and their impact on the allergic patient

Michael Hauser,1 Anargyros Roulias,1 Fátima Ferreira,1 and Matthias Egger1
1. Christian Doppler Laboratory for Allergy Diagnosis and Therapy, Department of Molecular Biology, University of Salzburg
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Abstract

The panallergen concept encompasses families of related proteins, which are involved in general vital processes and thus, widely distributed throughout nature. Plant panallergens share highly conserved sequence regions, structure, and function. They are responsible for many IgE cross-reactions even between unrelated pollen and plant food allergen sources. Although usually considered as minor allergens, sensitization to panallergens might be problematic as it bears the risk of developing multiple sensitizations. Clinical manifestations seem to be tightly connected with geographical and exposure factors. Future population- and disease-based screenings should provide new insights on panallergens and their contribution to disease manifestations. Such information requires molecule-based diagnostics and will be valuable for developing patient-tailored prophylactic and therapeutic approaches. In this article, we focus on profilins, non-specific lipid transfer proteins, polcalcins, and Bet v 1-related proteins and discuss possible consequences of panallergen sensitization for the allergic patient. Based on their pattern of IgE cross-reactivity, which is reflected by their distribution in the plant kingdom, we propose a novel classification of panallergens into ubiquitously spread “real panallergens” (e.g. profilins) and widespread “eurallergens” (e.g. polcalcins). “Stenallergens” display more limited distribution and cross-reactivity patterns, and “monallergens” are restricted to a single allergen source.

Taken together, understanding of immunologic cross-reactivity is essential to advance our knowledge about allergy. Additionally, this knowledge might help in the development of intelligent tools for the prediction of allergenicity of novel proteins or foods to which individuals previously have not been exposed. In fact, profilins, nsLTPs, and a Bet v 1 homologue were identified in vegetable varieties that were recently introduced to the European market.

Full text, graphs, charts and 81 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2830198/

European Journal Of Cancer Prevention • January 2010

Case-control study on beneficial effect of regular consumption of apples on colorectal cancer risk in a population with relatively low intake of fruits and vegetables

Author information

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Abstract

Laboratory in-vitro studies and animal experiments showing the potential health benefits from apples raises the question to what extent the regular consumption of apples in humans may have a beneficial effect on colorectal cancer risk. A total of 592 incident cases of colorectal cancer have been enrolled in a hospital-based case-control study. The comparison group included 765 controls chosen from the patients of the same hospital without history of cancer and admitted for treatment of nonneoplastic conditions. Interviews of both cases and controls were conducted in the hospital setting by trained interviewers. The median intake of fruits among cases was lower than in controls (9.5 vs. 11 servings/week) and the difference was statistically significant. Apples were the most frequent fruit consumed by the study participants and about 80% of variability in the total fruit consumption resulted from the intake of apples. We did not observe any significant statistical differences in consumption of berries, citrus, or stone fruits and other kinds of fruits across cases and controls. The adjusted estimates of colorectal cancer risk related to the daily consumption of apples (in quintiles) were based on the unconditional multivariate logistic model, which considered the set of potential confounding variables such as demographic characteristics of participants (age, gender, place of residency, marital status, tobacco smoking), total energy intake, intake of vegetables and fruits without apples. The results of the logistic analysis showed that the adjusted risk of colorectal cancer inversely correlated with daily number of apple servings. The reduced risk of colorectal cancer of border significance level was already observed at the consumption of at least one apple a day (odds ratio=0.65, 95% CI: 0.39-1.09), but at the intake of more than one apple a day the risk was reduced by about 50% (odds ratio=0.53, 95% CI: 0.35-0.79). Neither the consumption of vegetables nor other fruits have shown beneficial effects on the risk of colorectal cancer. The observed protective effect of apple consumption on colorectal risk may result from their rich content of flavonoid and other polyphenols, which can inhibit cancer onset and cell proliferation.

http://www.ncbi.nlm.nih.gov/pubmed/19926998

“The results of the logistic analysis showed that the adjusted risk of colorectal cancer inversely correlated with daily number of apple servings.

The reduced risk of colorectal cancer of border significance level was already observed at the consumption of at least one apple a day, but at the intake of more than one apple a day the risk was reduced by about 50%.

The observed protective effect of apple consumption on colorectal risk may result from their rich content of flavonoid and other polyphenols, which can inhibit cancer onset and cell proliferation.”

“High magnesium intake is associated with lower concentrations of certain markers of systemic inflammation and endothelial dysfunction in postmenopausal women.”

Diabetes Care • February 2010

Relations of dietary magnesium intaketo biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women

Author information
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Abstract

OBJECTIVE

Although magnesium may favorably affect metabolic outcomes, few studies have investigated the role of magnesium intake in systemic inflammation and endothelial dysfunction in humans.

RESULTS

After adjustment for age, ethnicity, clinical center, time of blood draw, smoking, alcohol, physical activity, energy intake, BMI, and diabetes status, magnesium intake was inversely associated with hs-CRP (P for linear trend = 0.003), IL-6 (P < 0.0001), TNF-alpha-R2 (P = 0.0006), and sVCAM-1 (P = 0.06). Similar findings remained after further adjustment for dietary fiber, fruit, vegetables, folate, and saturated and trans fat intake. Multivariable-adjusted geometric means across increasing quintiles of magnesium intake were 3.08, 2.63, 2.31, 2.53, and 2.16 mg/l for hs-CRP (P = 0.005); 2.91, 2.63, 2.45, 2.27, and 2.26 pg/ml for IL-6 (P = 0.0005); and 707, 681, 673, 671, and 656 ng/ml for sVCAM-1 (P = 0.04). An increase of 100 mg/day magnesium was inversely associated with hs-CRP (-0.23 mg/l +/- 0.07; P = 0.002), IL-6 (-0.14 +/- 0.05 pg/ml; P = 0.004), TNF-alpha-R2 (-0.04 +/- 0.02 pg/ml; P = 0.06), and sVCAM-1 (-0.04 +/- 0.02 ng/ml; P = 0.07). No significant ethnic differences were observed.

CONCLUSIONS

High magnesium intake is associated with lower concentrations of certain markers of systemic inflammation and endothelial dysfunction in postmenopausal women.

Full report with Graphs, Charts and 25 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2809271/

“Whole fruits of Hong Kong gordonia exhibited the strongest antioxidant capacity and had the second highest content of carotenoids. Seeds of Annona squamosa possessed the highest contents of total protein, fat and amino acids (17.6, 37.2 and 14.4%, respectively). Most peel and some seeds contained high levels of phenolics, carotenoids and vitamin C, which contributed to their strong antioxidant activity. Some of the fruits, peel or seeds from these Hong Kong plants can be a potential resource of functional components and nutraceuticals.”

Journal of Food Composition and Analysis • Horticulture, Biodiversity and Nutrition • March 2010

Survey of antioxidant capacity and nutritional quality of selected edible and medicinal fruit plants in Hong Kong

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Abstract

Twenty-two samples (including fruits, pulp, peel, or seeds) from 13 edible and medicinal fruit plant species selected in Hong Kong were investigated for their antioxidant capacity, nutritional quality and phenolic profiles. Significant variation existed among the tested samples in all the antioxidant and nutritional parameters. Proanthocyanidins, flavonoids and phenolic acids were identified as major categories of phenolic compounds in these samples. Whole fruits of Hong Kong gordonia exhibited the strongest antioxidant capacity (213.4 mmol trolox/100 g DW) and had the second highest content of carotenoids. Seeds of Annona squamosa possessed the highest contents of total protein, fat and amino acids (17.6, 37.2 and 14.4%, respectively). Most peel and some seeds contained high levels of phenolics, carotenoids and vitamin C, which contributed to their strong antioxidant activity. Some of the fruits, peel or seeds from these Hong Kong plants can be a potential resource of functional components and nutraceuticals.

Huang W.Y., Cai Y.Z., Corke H., Sun M. Survey of antioxidant capacity and nutritional quality of selected edible and medicinal fruit plants in Hong Kong. J. Food Compos. Anal. 2010;23:510–517. doi: 10.1016/j.jfca.2009.12.006.

www.sciencedirect.com/science/article/pii/S0889157510000475

Expert Reviews In Neurotherapy • May 2010

Oxidative stress and Alzheimer's disease: dietary polyphenols as potential therapeutic agents

Author information

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Abstract

"Oxidative stress has been strongly implicated in the pathophysiology of neurodegenerative disorders such as Alzheimer's disease (AD). In recent years, antioxidants - especially those of dietary origin - have been suggested as possible agents useful for the prevention and treatment of AD. This article reviews the role of oxidative stress and the contribution of free radicals in the development of AD, and also discusses the use of antioxidants as a therapeutic strategy in the amelioration of this illness. The antioxidant potential of polyphenolic compounds obtained from dietary sources, such as anthocyanins from berries, catechins and theaflavins from tea, curcumin from turmeric, resveratrol from grapes and peanuts, the dihydrochalcones aspalathin and nothofagin from rooibos and the xanthone mangiferin from honeybush, are discussed in this review. The neuroprotective effects of these phytochemicals in preclinical models of AD are highlighted. Finally, innovative concepts, novel hypotheses, current challenges and future directions in the use of dietary polyphenols for the treatment of AD are discussed."

http://www.ncbi.nlm.nih.gov/pubmed/20420493

As a result of the research activity that followed the publication of the prebiotic concept 15 years ago, it has become clear that products that cause a selective modification in the gut microbiota's composition and/or activity(ies) and thus strengthens normobiosis could either induce beneficial physiological effects in the colon and also in extra-intestinal compartments or contribute towards reducing the risk of dysbiosis and associated intestinal and systemic pathologies

British Journal Of Nutrition • August 2010

Prebiotic effects: metabolic and health benefits

Author information

Roberfroid M1, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A.
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Abstract

The different compartments of the gastrointestinal tract are inhabited by populations of micro-organisms. By far the most important predominant populations are in the colon where a true symbiosis with the host exists that is a key for well-being and health. For such a microbiota, 'normobiosis' characterises a composition of the gut 'ecosystem' in which micro-organisms with potential health benefits predominate in number over potentially harmful ones, in contrast to 'dysbiosis', in which one or a few potentially harmful micro-organisms are dominant, thus creating a disease-prone situation. The present document has been written by a group of both academic and industry experts (in the ILSI Europe Prebiotic Expert Group and Prebiotic Task Force, respectively). It does not aim to propose a new definition of a prebiotic nor to identify which food products are classified as prebiotic but rather to validate and expand the original idea of the prebiotic concept (that can be translated in 'prebiotic effects'), defined as: 'The selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host.' Thanks to the methodological and fundamental research of microbiologists, immense progress has very recently been made in our understanding of the gut microbiota. A large number of human intervention studies have been performed that have demonstrated that dietary consumption of certain food products can result in statistically significant changes in the composition of the gut microbiota in line with the prebiotic concept. Thus the prebiotic effect is now a well-established scientific fact. The more data are accumulating, the more it will be recognised that such changes in the microbiota's composition, especially increase in bifidobacteria, can be regarded as a marker of intestinal health. The review is divided in chapters that cover the major areas of nutrition research where a prebiotic effect has tentatively been investigated for potential health benefits. The prebiotic effect has been shown to associate with modulation of biomarkers and activity(ies) of the immune system. Confirming the studies in adults, it has been demonstrated that, in infant nutrition, the prebiotic effect includes a significant change of gut microbiota composition, especially an increase of faecal concentrations of bifidobacteria. This concomitantly improves stool quality (pH, SCFA, frequency and consistency), reduces the risk of gastroenteritis and infections, improves general well-being and reduces the incidence of allergic symptoms such as atopic eczema. Changes in the gut microbiota composition are classically considered as one of the many factors involved in the pathogenesis of either inflammatory bowel disease or irritable bowel syndrome. The use of particular food products with a prebiotic effect has thus been tested in clinical trials with the objective to improve the clinical activity and well-being of patients with such disorders. Promising beneficial effects have been demonstrated in some preliminary studies, including changes in gut microbiota composition (especially increase in bifidobacteria concentration). Often associated with toxic load and/or miscellaneous risk factors, colon cancer is another pathology for which a possible role of gut microbiota composition has been hypothesised. Numerous experimental studies have reported reduction in incidence of tumours and cancers after feeding specific food products with a prebiotic effect. Some of these studies (including one human trial) have also reported that, in such conditions, gut microbiota composition was modified (especially due to increased concentration of bifidobacteria). Dietary intake of particular food products with a prebiotic effect has been shown, especially in adolescents, but also tentatively in postmenopausal women, to increase Ca absorption as well as bone Ca accretion and bone mineral density. Recent data, both from experimental models and from human studies, support the beneficial effects of particular food products with prebiotic properties on energy homaeostasis, satiety regulation and body weight gain. Together, with data in obese animals and patients, these studies support the hypothesis that gut microbiota composition (especially the number of bifidobacteria) may contribute to modulate metabolic processes associated with syndrome X, especially obesity and diabetes type 2. It is plausible, even though not exclusive, that these effects are linked to the microbiota-induced changes and it is feasible to conclude that their mechanisms fit into the prebiotic effect. However, the role of such changes in these health benefits remains to be definitively proven. As a result of the research activity that followed the publication of the prebiotic concept 15 years ago, it has become clear that products that cause a selective modification in the gut microbiota's composition and/or activity(ies) and thus strengthens normobiosis could either induce beneficial physiological effects in the colon and also in extra-intestinal compartments or contribute towards reducing the risk of dysbiosis and associated intestinal and systemic pathologies.

http://www.ncbi.nlm.nih.gov/pubmed/20920376

Experimental Toxicology And Pathology • September 2010

Effect of rapeseed peptide on DNA damage and apoptosis in Hela cells

Author information

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Abstract

“Rapeseed peptide (RSP), obtained by hydrolyzing rapeseed protein, has anticancer activity. In this study, the effects of RSP on proliferation rate, morphological changes, DNA damage, cell cycle distribution and apoptosis in human cervical carcinoma (Hela) cells were investigated. RSP treatment at a concentration of 640 mg/L for 4 days inhibited Hela cell proliferation significantly, as determined by the MTT assay. We observed a dose-dependent increase in cytotoxicity induced by RSP at 20-640 mg/L. After 4 days of 320 mg/L RSP treatment, typical apoptotic changes were observed by transmission electron microscopy (TEM). Using the comet assay, we found dramatic comet tails, indicating DNA damage by RSP (20-640 mg/L). Moreover, RSP treatment caused inhibition of Hela cell growth, with cycle arrest in the S phase and apoptosis induction. **Taken together, the results suggested that rapeseed peptide could be a potential antitumor compound with an apoptotic mode of action.**”

http://www.ncbi.nlm.nih.gov/pubmed/19640692

“For some of the investigated minerals higher concentrations were observed in selections, primitive wheat, and old cultivars as compared to more modern wheat material, e.g., cultivars and spelt wheat.”

International Journal Of Environmental Research And Public Health • December 2010

Mineral Composition of Organically Grown Wheat Genotypes: Contribution to Daily Minerals Intake

Author Information

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Abstract

In this study, 321 winter and spring wheat genotypes were analysed for twelve nutritionally important minerals (B, Cu, Fe, Se, Mg, Zn, Ca, Mn, Mo, P, S and K). Some of the genotypes used were from multiple locations and years, resulting in a total number of 493 samples. Investigated genotypes were divided into six genotype groups i.e., selections, old landraces, primitive wheat, spelt, old cultivars and cultivars. For some of the investigated minerals higher concentrations were observed in selections, primitive wheat, and old cultivars as compared to more modern wheat material, e.g., cultivars and spelt wheat. Location was found to have a significant effect on mineral concentration for all genotype groups, although for primitive wheat, genotype had a higher impact than location. Spring wheat was observed to have significantly higher values for B, Cu, Fe, Zn, Ca, S and K as compared to winter wheat. Higher levels of several minerals were observed in the present study, as compared to previous studies carried out in inorganic systems, indicating that organic conditions with suitable genotypes may enhance mineral concentration in wheat grain. This study also showed that a very high mineral concentration, close to daily requirements, can be produced by growing specific primitive wheat genotypes in an organic farming system. Thus, by selecting genotypes for further breeding, nutritional value of the wheat flour for human consumption can be improved.

Full text, graphs, charts and 42 references

http://www.mdpi.com/1660-4601/7/9/3442/htm

“The risk of colorectal cancer was inversely correlated with daily number of apple servings, but the most significant reductions ... were observed for an intake one or more apple servings daily. No other fruit was significantly associated with altering the risk of colorectal cancer.”

Reviews In Environmental Health • January 2009

An apple a day may hold colorectal cancer at bay: recent evidence from a case-control study

Author information

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Abstract

Environmental factors play an important role in the etiology of colorectal cancer, the second-most common malignancy in both genders in developed countries. Evidence has shown that potential cancer-inducing oxidative damage might be prevented or restricted largely by the presence of dietary antioxidants of plant origin, such as fruits or vegetables. The protective antioxidant effect of fruits and vegetables has been attributed to flavonoids, a major class of phytochemicals naturally occurring in fruits, vegetables, and various foods of plant origin. Yet, epidemiologic cohort studies relating flavonoid intake to risk of colorectal cancer have been sparse and inconclusive. Apples are a rich source of flavonoids and have the second highest level of antioxidant power among all fruits, with peels having a stronger antioxidant activity than apple flesh. A recent reanalysis of several case-control studies in Italy demonstrated a consistent inverse association between apple consumption and the risk of various cancers, and among them of colorectal cancer. Here we assessed the potential protective impact of apples on risk of colorectal cancer in the course of a recently performed hospital-based case-control study in a country with dietary habits very different from those of Mediterranean region. The results showed that highest risk of colorectal cancer was among older persons and those who were residents of villages or small towns. The risk of colorectal cancer was inversely correlated with daily number of apple servings, but the most significant reductions of OR estimates were observed for an intake one or more apple servings daily (OR = 0.37, 95% CI: 0.15-0.91). No other fruit was significantly associated with altering the risk of colorectal cancer.

http://www.ncbi.nlm.nih.gov/pubmed/19476292

“All this effects neurotoxicity and promotes the development of various disorders, including depression. Vitamins B12 and B6, folic acid and omega-3 fatty acids supplementation is thus important in patients suffering from their deficiency; national diet as a significant factor in prevention of numerous CNS disorders, including depression, is also worth consideration.”

Polski Merkuriusz Lekarski • February 2009

Does diet affect our mood? The significance of folic acid and homocysteine

Author information

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Abstract

In recent years, there has been growing interest in the association between national diet and the possibility of developing various mental disorders, as well as between deficiency of such vitamins as, e.g. folic acid, vitamin B12, B6, and others (e.g., omega-3 fatty acids), elevated serum homocysteine level and the functioning of human brain as well as the occurrence of such disorders as dementia, central nervous system vascular disorders and depression.

THE AIM OF THE STUDY

was to present the current state of knowledge about the role of folic acid and homocysteine in the human organism as well as the significance of vitamin deficiency, mainly folic acid and hyperhomocysteinemy for the occurrence of mood disorders.

METHOD

The authors conducted the search of the Internet database Medline (www.pubmed.com) using as key words: depression, mood, homocysteine, vitamin deficiencies: folic acid, B6 and 812 and time descriptors: 1990-2007.

RESULTS

In depression, folate, vitamins B12 and B6, as well as unsaturated omega-3 fatty acids deficiency affects the biochemical processes in the CNS, as folic acid and vitamin B12, participate in the metabolism of S-adenosylmethionine (SAM), a donator of methyl groups, which play a decisive role in the functioning of the nervous system; they are, among others, active in the formation of neurotransmitters (e.g. serotonin), phospholipids that are a component of neuronal myelin sheaths, and cell receptors. The deficiency of the vitamins in question results in hyperhomocysteinemia (the research shows that approximately 45-55% of patients with depression develop significantly elevated serum homocysteine), which causes a decrease in SAM, followed by impaired methylation and, consequently, impaired metabolism of neurotransmitters, phospholipids, myelin, and receptors. Hyperhomocysteinemia also leads to activation of NMDA receptors, lesions in vascular endothelium, and oxidative stress. All this effects neurotoxicity and promotes the development of various disorders, including depression. Vitamins B12 and B6, folic acid and omega-3 fatty acids supplementation is thus important in patients suffering from their deficiency; national diet as a significant factor in prevention of numerous CNS disorders, including depression, is also worth consideration.

http://www.ncbi.nlm.nih.gov/pubmed/19388520

Chinese Medical Journal • June 2009

Hypoglycemic herbs and their action mechanisms

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Abstract

“Conventional drugs treat diabetes by improving insulin sensitivity, increasing insulin production and/or decreasing the amount of glucose in blood. Several herbal preparations are used to treat diabetes, but their reported hypoglycemic effects are complex or even paradoxical in some cases. This article reviews recent findings about some of the most popular hypoglycemic herbs, such as ginseng, bitter melon and Coptis chinensis. Several popular commercially available herbal preparations are also discussed, including ADHF (anti-diabetes herbal formulation), Jiangtangkeli, YGD (Yerbe Mate-Guarana-Damiana) and BN (Byakko-ka-ninjin-to). The efficacy of hypoglycemic herbs is achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from heptocytes.”

Full text, graphs, charts and 100 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2704217/

“In conclusion, the consumption of fruits, especially citrus, and cruciferous vegetables may protect against cerebrovascular diseases.”

British Journal Of Nutrition • October 2009

Plant foods and the risk of cerebrovascular diseases: a potential protection of fruit consumption

Author information

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Abstract

Studies on the association between plant foods and cerebrovascular diseases have given contradictory results suggesting the existence of some effect-modifying factors. The present study determines whether the consumption of plant foods (i.e. fruits and berries, vegetables, and cereals) predicts a decreased cerebrovascular disease incidence in a population with low fruit and vegetable and high wholegrain intake. This cohort study on 3932 men and women was based on data from the Finnish Mobile Clinic Health Examination Survey, conducted in 1968-72. The participants were 40-74 years of age and free of cardiovascular diseases at baseline. Data on the plant food consumption were derived from a 1-year dietary history interview. During a 24-year follow-up 625 cases of cerebrovascular diseases occurred, leading to either hospitalisation or death. An inverse association was found between fruit consumption and the incidence of cerebrovascular diseases, ischaemic stroke and intracerebral haemorrhage. The adjusted relative risks (RR) between the highest and lowest quartiles of intake of any cerebrovascular disease, ischaemic stroke and intracerebral haemorrhage were 0.75 (95 % CI 0.59, 0.94), 0.73 (95 % CI 0.54, 1.00) and 0.47 (95 % CI 0.24, 0.92), respectively. These associations were primarily due to the consumption of citrus fruits and occurred only in men. Total consumption of vegetables or cereals was not associated with the cerebrovascular disease incidence. The consumption of cruciferous vegetables, however, predicted a reduced risk of cerebrovascular diseases (RR 0.79; 95 % CI 0.63, 0.99), ischaemic stroke (RR 0.67; 95 % CI 0.49, 0.92) and intracerebral haemorrhage (RR 0.49; 95 % CI 0.25, 0.98). In conclusion, the consumption of fruits, especially citrus, and cruciferous vegetables may protect against cerebrovascular diseases.

http://www.ncbi.nlm.nih.gov/pubmed/19646291

“Significantly, much of the activity of Citrus flavonoids appears to impact blood and microvascular endothelial cells, and it is not surprising that the two main areas of research on the biological actions of Citrus flavonoids have been inflammation and cancer. Epidemiological and animal studies point to a possible protective effect of flavonoids against cardiovascular diseases and some types of cancer.”

Journal Of Agriculture And Food Chemistry • August 2008

Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity

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Abstract

Significantly, much of the activity of Citrus flavonoids appears to impact blood and microvascular endothelial cells, and it is not surprising that the two main areas of research on the biological actions of Citrus flavonoids have been inflammation and cancer. Epidemiological and animal studies point to a possible protective effect of flavonoids against cardiovascular diseases and some types of cancer. Although flavonoids have been studied for about 50 years, the cellular mechanisms involved in their biological action are still not completely known. Many of the pharmacological properties of Citrus flavonoids can be linked to the abilities of these compounds to inhibit enzymes involved in cell activation. Attempts to control cancer involve a variety of means, including the use of suppressing, blocking, and transforming agents. Suppressing agents prevent the formation of new cancers from procarcinogens, and blocking agents prevent carcinogenic compounds from reaching critical initiation sites, while transformation agents act to facilitate the metabolism of carcinogenic components into less toxic materials or prevent their biological actions. Flavonoids can act as all three types of agent. Many epidemiological studies have shown that regular flavonoid intake is associated with a reduced risk of cardiovascular diseases. In coronary heart disease, the protective effects of flavonoids include mainly antithrombotic, anti-ischemic, anti-oxidant, and vasorelaxant. It is suggested that flavonoids decrease the risk of coronary heart disease by three major actions: improving coronary vasodilatation, decreasing the ability of platelets in the blood to clot, and preventing low-density lipoproteins (LDLs) from oxidizing. The anti-inflammatory properties of the Citrus flavonoids have also been studied. Several key studies have shown that the anti-inflammatory properties of Citrus flavonoids are due to its inhibition of the synthesis and biological activities of different pro-inflammatory mediators, mainly the arachidonic acid derivatives, prostaglandins E 2, F 2, and thromboxane A 2. The anti-oxidant and anti-inflammatory properties of Citrus flavonoids can play a key role in their activity against several degenerative diseases and particularly brain diseases. The most abundant Citrus flavonoids are flavanones, such as hesperidin, naringin, or neohesperidin. However, generally, the flavones, such as diosmin, apigenin, or luteolin, exhibit higher biological activity, even though they occur in much lower concentrations. Diosmin and rutin have a demonstrated activity as a venotonic agent and are present in several pharmaceutical products. Apigenin and their glucosides have been shown a good anti-inflammatory activity without the side effects of other anti-inflammatory products. In this paper, we discuss the relation between each structural factor of Citrus flavonoids and the anticancer, anti-inflammatory, and cardiovascular protection activity of Citrus flavonoids and their role in degenerative diseases.

http://www.ncbi.nlm.nih.gov/pubmed/18593176

“The review identifies trial design elements specifically applicable to polyphenolic phytochemicals. The available evidence for tea polyphenols tentatively supports their advancement into phase III clinical intervention trials aimed at the prevention of progression of prostate intraepithelial neoplasia, leukoplakia or premalignant cervical disease. In the case of curcumin and soya isoflavones more studies in premalignacies seem appropriate to optimise the nature and design of suitable phase III trials. The abundance of flavonoids and related polyphenols in the plant kingdom makes it possible that several hitherto uncharacterised agents with chemopreventive efficacy are still to be identified, which may constitute attractive alternatives to currently used chemopreventive drugs.”

International Journal Of Cancer • February 2007

Dietary polyphenolic phytochemicals—promising cancer chemopreventive agents in humans? A review of their clinical properties

Author information
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Abstract

Epidemiological and preclinical evidence suggests that polyphenolic phytochemicals exemplified by epigallocatechin gallate from tea, curcumin from curry and soya isoflavones possess cancer chemopreventive properties. Whilst such naturally occurring polyphenols have been the subject of numerous mechanistic studies in cells, information on their clinical properties, which might help assess their promise as human cancer chemopreventive agents, is scarce. Therefore, we present a review of pilot studies and trials with a cancer chemoprevention-related rationale, in which either healthy individuals or patients with premalignant conditions or cancer received polyphenolic phytochemicals. The review identifies trial design elements specifically applicable to polyphenolic phytochemicals. The available evidence for tea polyphenols tentatively supports their advancement into phase III clinical intervention trials aimed at the prevention of progression of prostate intraepithelial neoplasia, leukoplakia or premalignant cervical disease. In the case of curcumin and soya isoflavones more studies in premalignacies seem appropriate to optimise the nature and design of suitable phase III trials. The abundance of flavonoids and related polyphenols in the plant kingdom makes it possible that several hitherto uncharacterised agents with chemopreventive efficacy are still to be identified, which may constitute attractive alternatives to currently used chemopreventive drugs.

Full text, graphs, charts and 83 references

http://onlinelibrary.wiley.com/doi/10.1002/ijc.22419/epdf

Journal Of Agricultural And Food Chemistry • February 2007

Carotenoid absorption in humans consuming tomato sauces obtained from tangerine or high-beta-carotene varieties of tomatoes

Author information

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Abstract

“Tomato sauces were produced from unique tomato varieties to study carotenoid absorption in humans. Tangerine tomatoes, high in cis-lycopene, especially prolycopene (7Z,9Z,7'Z,9'Z), and high-beta-carotene tomatoes as an alternative dietary source of beta-carotene were grown and processed. Sauces were served after 2 week washout periods and overnight fasting for breakfast to healthy subjects (n = 12, 6M/6F) in a randomized crossover design. The serving size was 150 g (containing 15 g of corn oil), tangerine sauce containing 13 mg of lycopene (97.0% as cis-isomers) and high-beta-carotene sauce containing 17 mg of total beta-carotene (1.6% as the 9-cis-isomer) and 4 mg of lycopene. Blood samples were collected 0, 2, 3, 4, 5, 6, 8, and 9.5 h following test meal consumption and carotenoids determined in the plasma triacylglycerol-rich lipoprotein fraction by HPLC-electrochemical detection. Baseline-corrected areas under the concentration vs time curves (AUC) were used as a measure of absorption. AUC0-9.5h values for total lycopene in the tangerine sauce group were 870 +/- 187 (nmol.h)/L (mean +/- SEM) with >99% as cis-isomers (59% as the tetra-cis-isomer). The AUC0-9.5h values for total beta-carotene and lycopene after consumption of the high-beta-carotene sauce were 304 +/- 54 (4% as 9-cis-carotene) and 118 +/- 24 (nmol.h)/L, respectively. Lycopene dose-adjusted triacylglycerol-rich lipoprotein AUC responses in the tangerine sauce group were relatively high when compared to those in the literature and the high-beta-carotene group. The results support the hypothesis that lycopene cis-isomers are highly bioavailable and suggest that special tomato varieties can be utilized to increase both the intake and bioavailability of health-beneficial carotenoids.”

http://www.ncbi.nlm.nih.gov/pubmed/17243700

British Journal Of Nutrition • July 2007

Lycopene from heat-induced cis-isomer-rich tomato sauce is more bioavailable than from all-trans-rich tomato sauce in human subjects

Author information

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Abstract

“Lycopene is present mainly as cis-isomers in human serum and tissues whereas all-trans-lycopene predominates in tomato products, suggesting that all-trans-lycopene is isomerised in the body or is less bioavailable. The objectives of the present study were to develop processing conditions for tomatoes to obtain products with different cis-trans-lycopene isomer distribution and to assess their bioavailability. Healthy adult subjects (n 12) were recruited for this randomised cross-over trial. Each intervention was preceded by a 2-week washout period. Two tomato sauces, one rich in all-trans-lycopene (32.5 mg total lycopene/100 g sauce; 5 % cis-isomers), the other high in cis-lycopene (26.4 mg total lycopene/100 g sauce; 45 % cis-isomers), were produced by different heat-processing techniques. Each sauce (150 g) was served in a standardised meal at 08.00 hours after overnight fasting. Plasma TAG-rich lipoprotein fractions over 9.5 h following test-meal consumption as a measure of lycopene absorption were obtained and expressed as baseline-corrected area under the concentration v. time curves (AUC), using HPLC-electrochemical detection. AUC values adjusted for the amount lycopene consumed showed that total, total cis-, and all-trans-lycopene responses were significantly higher from the cis-isomer-rich sauce, compared with the all-trans-rich sauce, being 7.30 (sem 1.45) v. 4.74 (sem 1.08) nmol x h/l (P = 0.002), 3.80 (sem 0.76) v. 1.98 (sem 0.37) nmol x h/l (P = 0.0005) and 3.50 (sem 0.76) v. 2.76 (sem 0.76) nmol x h/l (P = 0.01), respectively. The present study demonstrates significant lycopene bioavailability from cis-lycopene-rich tomato sauce and highlights the importance of considering isomer-distribution for lycopene bioavailability. Furthermore, processing parameters can be controlled to alter isomer patterns of tomato products and influence lycopene bioavailability.”

http://www.ncbi.nlm.nih.gov/pubmed/17391568

“It is important to recognize that this is only a crude range of estimates and that the proportion of cancers that might be preventable by increasing fruit and vegetable intake may vary beyond this range for specific cancer sites and across different regions of the world.”

Nutrition And Cancer • July 2006

Fruit and vegetables in cancer prevention

Author information

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Abstract

Our aim was to review the epidemiological literature on possible cancer-preventive effects of the consumption of fruits and vegetables in humans, to quantify the effect of high versus low consumption of fruits and vegetables, and to give an overall assessment of the existing evidence. We based our work on an expert meeting conducted by the International Agency for Research on Cancer in 2003. A qualitative reading and evaluation of relevant articles on the cancer-preventive effect of the consumption of fruits and vegetables was made followed by the calculation of the mean relative risk and range for cohort and case-control studies separately. The possible population-preventable fraction for modifying diet in relation to fruit and vegetable consumption was calculated as well as an overall statement about the degree of evidence for the cancer-preventive effect of fruit and vegetable consumption for each cancer site. There is limited evidence for a cancer-preventive effect of the consumption of fruits and vegetables for cancer of the mouth and pharynx, esophagus, stomach, colon-rectum, larynx, lung, ovary (vegetables only), bladder (fruit only), and kidney. There is inadequate evidence for a cancer-preventive effect of the consumption of fruits and vegetables for all other sites. Applying this range of risk difference to the range of prevalence of low intake, the preventable fraction for low fruit and vegetable intake would fall into the range of 5-12%. It is important to recognize that this is only a crude range of estimates and that the proportion of cancers that might be preventable by increasing fruit and vegetable intake may vary beyond this range for specific cancer sites and across different regions of the world.

http://www.ncbi.nlm.nih.gov/pubmed/16800779

European Journal Of Pharmacology • September 2006

Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets

By C. Ramassamy

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Abstract

"Aging is the major risk factor for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. A large body of evidence indicates that oxidative stress is involved in the pathophysiology of these diseases. Oxidative stress can induce neuronal damages, modulate intracellular signaling, ultimately leading to neuronal death by apoptosis or necrosis. Thus antioxidants have been studied for their effectiveness in reducing these deleterious effects and neuronal death in many in vitro and in vivo studies. Increasing number of studies demonstrated the efficacy of polyphenolic antioxidants from fruits and vegetables to reduce or to block neuronal death occurring in the pathophysiology of these disorders. These studies revealed that other mechanisms than the antioxidant activities could be involved in the neuroprotective effect of these phenolic compounds. We will review some of these mechanisms and particular emphasis will be given to polyphenolic compounds from green tea, the Ginkgo biloba extract EGb 761, blueberries extracts, wine components and curcumin."

http://www.ncbi.nlm.nih.gov/pubmed/16904103

“In Denmark it is recommended to eat 600 g of fruit and vegetables daily. This recommendation has to a large extent been derived from the demonstrated inverse association with the risk of certain major cancer diseases, while the focus with respect to prevention of ischemic heart disease (IHD) has been directed primarily towards a reduced intake of ‘’hard’’ fats. Based on the studies, it seems reasonable to recommend an increased intake of a mix of fruits and vegetables to reduce the risk of ischemic heart disease. The maximum beneficial amount seems to be about 800 grams per day.”

Ugeskrift For Laeger • June 2005

Increased consumption of fruits and vegetables reduces the risk of ischemic heart disease

Author information
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Abstract

In Denmark it is recommended to eat 600 g of fruit and vegetables daily. This recommendation has to a large extent been derived from the demonstrated inverse association with the risk of certain major cancer diseases, while the focus with respect to prevention of ischemic heart disease (IHD) has been directed primarily towards a reduced intake of ‘’hard’’ fats. This systematic review includes prospective studies which have examined the association between the intake of fruit and vegetables, as well as specific fruits and vegetables (e.g., nuts and pulses, which are considered to be fruits and vegetables in the Danish recommendations), and the risk of developing IHD. Only one controlled intervention study has been performed. This study came out with a negative result because the advice to increase intake was unsuccessful. In the eight published cohort studies, the overall finding was that the risk of developing IHD was reduced, in the scientifically well-conducted studies, by about 20%. Studies have generally found a dose-response effect, from low intakes to high intakes, up to about 800 g daily. Large cohort studies have shown convincing evidence that increased intake of nuts reduces the risk of IHD. With respect to other groups of fruits and vegetables, there is good but not sufficient scientific evidence that particularly pulses, but also the group of carotenoid-rich fruit and vegetables (such as tomatoes, leafy green vegetables, carrots, broccoli, Brussels sprouts and many berries and fruits), reduces risk. In contrast, it is not possible to single out specific substances in fruit and vegetables as being beneficial. Based on the studies, it seems reasonable to recommend an increased intake of a mix of fruits and vegetables to reduce the risk of IHD. The maximum beneficial amount seems to be about 800 g per day.

http://www.ncbi.nlm.nih.gov/pubmed/16014256

Ugeskrift For Laeger • June 2005

Is a high intake of fruits and vegetables related to a lowered risk of cerebrovascular disease?

Author information

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Abstract

"The scientific evidence for a beneficial effect of an increased intake of fruits and vegetables rests on nine cohort studies. All cohort studies have shown a risk reduction in groups with high intakes of vegetables and/or fruits compared to groups with low intakes. The risk reduction has been about 30% in the scientifically best conducted studies. Further, many studies have demonstrated a dose-response association. It is not known if specific vegetables and fruits, or single nutrients alone, are particularly beneficial. A high intake of vegetables and fruits to reduce the risk of stroke should therefore be recommended."

http://www.ncbi.nlm.nih.gov/pubmed/16014257

Cancer Epidemiology And Biomarkers Prevention • June 2005

Diet and cancer: the disconnect between epidemiology and randomized clinical trials

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Abstract

Dietary epidemiology has been highly successful in identifying the responsible agent in many diseases, including scurvy, pellagra, blindness, and spinal bifida. Case-control, cohort, and ecologic observational studies have consistently associated increased consumption of fruits and vegetables with a decreased risk for a wide variety of epithelial cancers and, in many cases, specific dietary components seem to decrease the risk for a wide array of epithelial cancers. Over time, there has been enthusiasm for one or another compounds, such as beta-carotene in the past and folate currently. Despite the success of translating similar epidemiologic observations to clinical benefit in other areas of medicine via the crucible of the randomized clinical trial, this strategy has not been nearly as successful for cancer. We propose that the inability of nutritional epidemiology to identify effective chemopreventive strategies is not just a problem of quantitation, but rather that the discipline is usually qualitatively incapable of identifying a dietary compound(s) that will be efficacious. One needs to consider the following basic questions in trying to understand why nutritional epidemiology has not been translated into progress in cancer prevention: Why do fruits and vegetable show a consistent protective effect against many epithelial cancers in epidemiologic studies? Once a specific dietary compound is identified as protective in observational studies, why do most subsequent observational studies confirm the effect? Why are dietary epidemiology observations frequently not confirmed by the randomized clinical trial? We call the identified problems “fishing with only one bait” and the “four-legged stool problem.” The considerations identified in this analysis offer a number of possible solutions to puzzling findings: (a) Fruits and vegetables consistently show a protective effect against cancer in observational studies because they represent the entire “biological action package.” (b) Dietary compounds show a protective effect in observational studies, but not in clinical trials, because this is an inevitable consequence of one compound being falsely identified as the active agent in a system in which multiple agents or multiple interacting regulatory molecules underlie the biological effect. The consequences are serious for trying to use epidemiology to identify effective nutritional compounds. The major conclusion has to be as follows: Supplementation with single dietary compounds is rarely going to be as effective as epidemiologic studies suggest; it is the biological action package that determines efficacy. Options for how we should move forward will be discussed. Dietary observational epidemiology is complex and involves many biases and confounders. We need to be more critical in the design of large randomized trials based on observational epidemiology or analysis. Rules of evidence are frequently ignored or misunderstood although the limitations of observational epidemiology are analogous to the problems associated with discovery-based research and biomarker identification. We need to be much more self-critical in the important and critical assessment of dietary compounds and their role in cancer prevention given the very high appeal for this approach both within the lay and scientific communities.

Full text with 20 references

http://cebp.aacrjournals.org/content/14/6/1366.long

Metabolism • November 2005

Raw vegetable food containing high cyclo (his-pro) improved insulin sensitivity and body weight control

Author information

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Abstract

Cyclo (his-pro), controlled-energy diet, soy protein hydrolysate (SPH), and raw vegetable food (RVF) are known to improve insulin sensitivity and body weight (BW) control. Enhancement of high cyclo (his-pro) content in SPH (HCS) was performed by refluxing SPH with 1 N KH(2)CO(3) dissolved in 70% ethanol for 2 weeks at room temperature. Using this material, we examined the effects of HCS plus RVF on glucose metabolism and BW control in genetically diabetic Goto-Kakizaki (G-K) and insulin-resistant aged overweight Sprague-Dawley (S-D) rats. Thirty 7-week-old G-K rats and 18 16- to 18-month-old S-D rats were divided into 3 groups and treated with normal chow (NC), RVF diet, or HCS diet for 8 weeks. Raw vegetable food diet was made of 1:3 RVF and 2:3 NC; HCS diet was made of 1:27 portion HCS, 8:27 RVF, and 2:3 NC. Oral glucose tolerance significantly improved in both RVF- ($P<.01$) and HCS-treated ($P<.001$) G-K rats and worsened in NC-fed rats compared with the baseline values. Similarly, oral glucose tolerance also improved in aged overweight S-D rats when treated with RVF ($P<.05$) and with HCS ($P<.01$), compared with the baseline values. Although HCS diet treatment very significantly lowered fed plasma insulin levels compared with NC diet treatment in G-K rats ($P<.01$), RVF diet treatment alone did not decrease plasma insulin levels. In contrast, there was no change of insulin levels in overweight aged S-D rats after either RVF or HCS diet treatment. Postfeeding glucose levels in G-K rats fed RVF or HCS significantly fell, compared with the rats fed NC ($P<.05$). Interestingly, fasting blood glucose levels in RVF- or HCS-fed rats were very significantly lower than in NC-fed rats ($P<.001$). There was no change of blood glucose levels in S-D rats due to treatments with different diet. In G-K rats, food intake did not decrease during the first 3 weeks but fell very significantly from the fifth to eighth weeks with RVF ($P<.01$) and HCS ($P<.001$) treatments in G-K rats. However, food intake reduction in aged S-D rats was shown only for the HCS-treated rat group ($P<.05$). Water intake slightly decreased in G-K rats with either RVF or HCS treatment ($P<.05$) but very significantly decreased in S-D rats with HCS treatment ($P<.01$). Body weight gain in young G-K rats and BW in aged S-D rats significantly decreased only when rats were treated with HCS diet ($P<.05$). These data suggest that regular consumption of HCS diet helps to control blood glucose metabolism in diabetic G-K rats and BW control in aged obese S-D rats.

http://www.ncbi.nlm.nih.gov/pubmed/16253637

Critical Reviews In Food Science And Nutrition • July 2004

Antioxidants and prevention of chronic disease

Author information

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Abstract

"The generation of reactive oxygen species (ROS) and other free radicals (R) during metabolism is a necessary and normal process that ideally is compensated for by an elaborate endogenous antioxidant system. However, due to many environmental, lifestyle, and pathological situations, excess radicals can accumulate, resulting in oxidative stress. Oxidative stress has been related to cardiovascular disease, cancer, and other chronic diseases that account for a major portion of deaths today. Antioxidants are compounds that hinder the oxidative processes and thereby delay or prevent oxidative stress. This article examines the process of oxidative stress and the pathways by which it relates to many chronic diseases. We also discuss the role that endogenous and exogenous antioxidants may play in controlling oxidation and review the evidence of their roles in preventing disease."

http://www.ncbi.nlm.nih.gov/pubmed/15462130

“Thus, there is strong evidence to suggest that eating a variety of whole grain foods and legumes is beneficial in the prevention and management of diabetes. This is compatible with advice from around the world that recommends consumption of a wide range of carbohydrate foods from cereals, vegetables, legumes and fruits both for the general population and for people with diabetes.”

European Journal Of Clinical Nutrition • November 2004

Cereal grains, legumes and diabetes

Author information
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Abstract

This review examines the evidence for the role of whole grain foods and legumes in the aetiology and management of diabetes. MedLine and SilverPlatter (‘Nutrition’ and ‘Food Science FSTA’) databases were searched to identify epidemiological and experimental studies relating to the effects of whole grain foods and legumes on indicators of carbohydrate metabolism. Epidemiological studies strongly support the suggestion that high intakes of whole grain foods protect against the development of type II diabetes mellitus (T2DM). People who consume approximately 3 servings per day of whole grain foods are less likely to develop T2DM than low consumers (<3 servings per week) with a risk reduction in the order of 20-30%. The role of legumes in the prevention of diabetes is less clear, possibly because of the relatively low intake of leguminous foods in the populations studied. However, legumes share several qualities with whole grains of potential benefit to glycaemic control including slow release carbohydrate and a high fibre content. A substantial increase in dietary intake of legumes as replacement food for more rapidly digested carbohydrate might therefore be expected to improve glycaemic control and thus reduce incident diabetes. This is consistent with the results of dietary intervention studies that have found improvements in glycaemic control after increasing the dietary intake of whole grain foods, legumes, vegetables and fruit. The benefit has been attributed to an increase in soluble fibre intake. However, prospective studies have found that soluble fibre intake is not associated with a lower incidence of T2DM. On the contrary, it is cereal fibre that is largely insoluble that is associated with a reduced risk of developing T2DM. Despite this, the addition of wheat bran to the diets of diabetic people has not improved indicators of glycaemic control. These apparently contradictory findings might be explained by metabolic studies that have indicated improvement in glucose handling is associated with the intact structure of food. For both grains and legumes, fine grinding disrupts cell structures and renders starch more readily accessible for digestion. The extent to which the intact structure of grains and legumes or the composition of foods in terms of dietary fibre and other constituents contribute to the beneficial effect remains to be quantified. Other mechanisms to help explain improvements in glycaemic control when consuming whole grains and legumes relate to cooking, type of starch, satiety and nutrient retention. Thus, there is strong evidence to suggest that eating a variety of whole grain foods and legumes is beneficial in the prevention and management of diabetes. This is compatible with advice from around the world that recommends consumption of a wide range of carbohydrate foods from cereals, vegetables, legumes and fruits both for the general population and for people with diabetes.

http://www.ncbi.nlm.nih.gov/pubmed/15162131

“Parsley is used by diabetics in Turkey to reduce blood glucose ... The present study suggests that parsley demonstrates a significant hepatoprotective effect in diabetic rats.”

Phytotherapeutics Research • December 2004

Effects of parsley (Petroselinum crispum) on the liver of diabetic rats: a morphological and biochemical study

Author information

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Abstract

Parsley is used by diabetics in Turkey to reduce blood glucose. The present study aims to investigate both the morphological and biochemical effects of parsley on liver tissue. Rat hepatocytes were examined by light and electron microscopy. Degenerative changes were observed in the hepatocytes of diabetic rats. These degenerative changes were significantly reduced or absent in the hepatocytes of diabetic rats treated with parsley. Blood glucose levels, alanine transaminase and alkaline phosphatase were observed to be raised in diabetic rats. Diabetic rats treated with parsley demonstrated significantly lower levels of blood glucose, alanine transaminase and alkaline phosphatase. The present study suggests that parsley demonstrates a significant hepatoprotective effect in diabetic rats.

http://www.ncbi.nlm.nih.gov/pubmed/15742348

“Consequently, the findings of this work indicate that diets that are rich in plant-derived foods can promote longevity.”

Journal Of Nutrition • January 2003

Low intake of fruits, berries and vegetables is associated with excess mortality in men: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study

Author information

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Abstract

Diets rich in fruits and vegetables have been of interest because of their potential health benefits against chronic diseases such as cardiovascular disease (CVD) and cancer. The aim of this work was to assess the association of the dietary intake of a food group that includes fruits, berries and vegetables with all-cause, CVD-related and non-CVD-related mortality. The subjects were Finnish men aged 42-60 y examined in 1984-1989 in the prospective Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. Dietary intakes were assessed by 4-d food intake record during the baseline phase of the KIHD Study. The risk of all-cause and non-CVD-related deaths was studied in 2641 men and the risk of CVD-related death in 1950 men who had no history of CVD at baseline. During a mean follow-up time of 12.8 y, cardiovascular as well as noncardiovascular and all-cause mortality were lower among men with the highest consumption of fruits, berries and vegetables. After adjustment for the major CVD risk factors, the relative risk for men in the highest fifth of fruit, berry and vegetable intake for all-cause death, CVD-related and non-CVD-related death was 0.66 [95% confidence interval (CI) 0.50-0.88], 0.59 (0.33-1.06), and 0.68 (0.46-1.00), respectively, compared with men in the lowest fifth. These data show that a high fruit, berry and vegetable intake is associated with reduced risk of mortality in middle-aged Finnish men. Consequently, the findings of this work indicate that diets that are rich in plant-derived foods can promote longevity.

http://www.ncbi.nlm.nih.gov/pubmed/12514290

“The few whole-grain feeding studies that are available show improvements in biomarkers with whole-grain consumption, such as weight loss, blood lipid improvement and antioxidant protection.”

The Proceedings Of The Nutrition Society • February 2003

Why whole grains are protective: biological mechanisms

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Abstract

Epidemiological studies find that whole-grain intake is protective against cancer, cardiovascular disease, diabetes and obesity. Potential mechanisms for this protection are diverse since whole grains are rich in nutrients and phytochemicals. First, whole grains are concentrated sources of dietary fibre, resistant starch and oligosaccharides, carbohydrates that escape digestion in the small intestine and are fermented in the gut, producing short-chain fatty acids (SCFA). SCFA lower colonic pH, serve as an energy source for the colonocytes and may alter blood lipids. These improvements in the gut environment may provide immune protection beyond the gut. Second, whole grains are rich in antioxidants, including trace minerals and phenolic compounds, and these compounds have been linked to disease prevention. Additionally, whole grains mediate insulin and glucose responses. Although lower glycaemic load and glycaemic index have been linked to diabetes and obesity, risk of cancers such as colon and breast cancer have also been linked to high intake of readily-available carbohydrate. Finally, whole grains contain many other compounds that may protect against chronic disease. These compounds include phytate, phyto-oestrogens such as lignan, plant stanols and sterols, and vitamins and minerals. As a consequence of the traditional models of conducting nutrition studies on isolated nutrients, few studies exist on the biological effects of increased whole-grain intake. The few whole-grain feeding studies that are available show improvements in biomarkers with whole-grain consumption, such as weight loss, blood lipid improvement and antioxidant protection.

http://www.ncbi.nlm.nih.gov/pubmed/12740067

“Whole grain consumption has been associated with reduced risk of chronic diseases, such as cardiovascular diseases and cancer. These beneficial effects have been attributed to the unique phytochemicals of grains that complement those found in fruits and vegetables. Wheat is one of the major grains in the human diet ...”

Journal Of Agriculture And Food Chemistry • December 2003

Phytochemical profiles and antioxidant activity of wheat varieties

Author information

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Abstract

Whole grain consumption has been associated with reduced risk of chronic diseases, such as cardiovascular diseases and cancer. These beneficial effects have been attributed to the unique phytochemicals of grains that complement those found in fruits and vegetables. Wheat is one of the major grains in the human diet; however, little is known about the inherent varietal differences in phytochemical profiles, total phenolic and carotenoid contents, or total antioxidant activities of different wheat varieties, which ultimately influence the associated nutritional and health benefits of wheat and wheat products. The objectives of this study were to determine the phytochemical profiles and total antioxidant activity for 11 diverse wheat varieties and experimental lines. The profiles included free, soluble-conjugated, and insoluble-bound forms of total phenolics, flavonoids, and ferulic acids and carotenoid content including lutein, zeaxanthin, and beta-cryptoxanthin. The results showed that total phenolic content (709.8-860.0 micromol of gallic acid equiv/100 g of wheat), total antioxidant activity (37.6-46.4 micromol of vitamin C/g), and total flavonoid content (105.8-141.8 micromol of catechin equiv/100 g of wheat) did not vary greatly among the 11 wheat lines. However, significant differences in total ferulic acid content ($p < 0.05$) and carotenoid content ($p < 0.05$) among the varieties were observed, with carotenoid content exhibiting the greatest range of values. Carotenoid content among the 11 wheat varieties exhibited 5-fold, 3-fold, and 12-fold differences in lutein, zeaxanthin, and beta-cryptoxanthin, respectively. A synthetic wheat experimental line, W7985, gave the lowest carotenoid concentrations of any of the genotypes in this study. Such large genotypic differences in carotenoid content may open up new opportunities for breeding wheat varieties with higher nutritional value.

http://www.ncbi.nlm.nih.gov/pubmed/14664553

Presse Medicale • July 2002

Antioxidants To Slow Aging, Facts And Perspectives

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Abstract

FREE RADICALS AND THE THEORY OF AGING

Severe oxidative stress progressively leads to cell dysfunction and ultimately cell death. Oxidative stress is defined as an imbalance between pro-oxidants and/or free radicals on the one hand, and anti-oxidizing systems on the other. The oxygen required for living may indirectly be responsible for negative effects; these deleterious effects are due to the production of free radicals, which are toxic for the cells (superoxide anions, hydroxyl radicals, peroxyl radicals, hydrogen peroxide, hydroperoxides and peroxinitrite anions). Free radical attacks are responsible for cell damage and the targeted cells are represented by the cell membranes, which are particularly rich in unsaturated fatty acids, sensitive to oxidation reactions; DNA is also the target of severe attacks by these reactive oxygen species (ROS).

THE DEFENCE SYSTEMS

These are represented by the enzymes and free radical captors. The latter are readily oxidizable composites. The free radical captor or neutralization systems of these ROS use a collection of mechanisms, vitamins (E and C), enzymes [superoxide dismutase (SOD), glutathion peroxidase (GPx) and others], and glutathion reductase (GSH), capable of neutralizing peroxinitrite. The efficacy of this system is dependent on the genome for the enzymatic defence systems, and on nutrition for the vitamins. Some strategies aimed at reducing oxidative stress-related alterations have been performed in animals. However, only a few can be used and are efficient in humans, such as avoidance of unfavourable environmental conditions (radiation, dietary carcinogens, smoking...) and antioxidant dietary supplementation.

DIETARY SUPPLEMENTATION

Epidemiological data suggest that antioxidants may have a beneficial effect on many age-related diseases: atherosclerosis, cancer, some neurodegenerative and ocular diseases. However, the widespread use of supplements is hampered by several factors: the lack of prospective and controlled studies; insufficient knowledge on the pro-oxidant, oxidant and ant-oxidant properties of the various supplements; growing evidence that free radicals are not only by-products, but also play an important role in cell signal transduction, apoptosis and infection control.

RECOMMENDATIONS

Although current data indicate that antioxidants cannot prolong maximal life span, the beneficial impact of antioxidants on various age-related degenerative diseases may forecast an improvement in life span and enhance quality of life. The current lack of sufficient data does not permit the systematic recommendation of anti-oxidants. Nevertheless, antioxidant-rich diets with fruit and vegetables should be recommended.

http://www.ncbi.nlm.nih.gov/pubmed/12192730

“Bound phytochemicals were the major contributors to the total antioxidant activity: 90% in wheat, 87% in corn, 71% in rice, and 58% in oats. Bound phytochemicals could survive stomach and intestinal digestion to reach the colon. This may partly explain the mechanism of grain consumption in the prevention of colon cancer, other digestive cancers, breast cancer, and prostate cancer, which is supported by epidemiological studies.”

Journal Of Agriculture And Food Chemistry • October 2002

Antioxidant activity of grains

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Abstract

Epidemiological studies have shown that consumption of whole grains and grain-based products is associated with reduced risk of chronic diseases. The health benefits of whole grains are attributed in part to their unique phytochemical composition. However, the phytochemical contents in grains have been commonly underestimated in the literature, because bound phytochemicals were not included. This study was designed to investigate the complete phytochemical profiles in free, soluble conjugated, and insoluble bound forms, as well as their antioxidant activities in uncooked whole grains. Corn had the highest total phenolic content (15.55 +/- 0.60 micromol of gallic acid equiv/g of grain) of the grains tested, followed by wheat (7.99 +/- 0.39 micromol of gallic acid equiv/g of grain), oats (6.53 +/- 0.19 micromol of gallic acid equiv/g of grain), and rice (5.56 +/- 0.17 micromol of gallic acid equiv/g of grain). The major portion of phenolics in grains existed in the bound form (85% in corn, 75% in oats and wheat, and 62% in rice), although free phenolics were frequently reported in the literature. Ferulic acid was the major phenolic compound in grains tested, with free, soluble-conjugated, and bound ferulic acids present in the ratio 0.1:1:100. Corn had the highest total antioxidant activity (181.42 +/- 0.86 micromol of vitamin C equiv/g of grain), followed by wheat (76.70 +/- 1.38 micromol of vitamin C equiv/g of grain), oats (74.67 +/- 1.49 micromol of vitamin C equiv/g of grain), and rice (55.77 +/- 1.62 micromol of vitamin C equiv/g of grain). Bound phytochemicals were the major contributors to the total antioxidant activity: 90% in wheat, 87% in corn, 71% in rice, and 58% in oats. Bound phytochemicals could survive stomach and intestinal digestion to reach the colon. This may partly explain the mechanism of grain consumption in the prevention of colon cancer, other digestive cancers, breast cancer, and prostate cancer, which is supported by epidemiological studies.

http://www.ncbi.nlm.nih.gov/pubmed/12358499

Pharmacology & Therapeutics • November 2002

The biochemistry and medical significance of the flavonoids

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Abstract

“Flavonoids are plant pigments that are synthesised from phenylalanine, generally display marvelous colors known from flower petals, mostly emit brilliant fluorescence when they are excited by UV light, and are ubiquitous to green plant cells. The flavonoids are used by botanists for taxonomical classification. They regulate plant growth by inhibition of the exocytosis of the auxin indolyl acetic acid, as well as by induction of gene expression, and they influence other biological cells in numerous ways. Flavonoids inhibit or kill many bacterial strains, inhibit important viral enzymes, such as reverse transcriptase and protease, and destroy some pathogenic protozoans. Yet, their toxicity to animal cells is low. Flavonoids are major functional components of many herbal and insect preparations for medical use, e.g., propolis (bee’s glue) and honey, which have been used since ancient times. The daily intake of flavonoids with normal food, especially fruit and vegetables, is 1-2 g. Modern authorised physicians are increasing their use of pure flavonoids to treat many important common diseases, due to their proven ability to inhibit specific enzymes, to simulate some hormones and neurotransmitters, and to scavenge free radicals.”

http://www.ncbi.nlm.nih.gov/pubmed/12453566

“Despite their widespread use in food products, few reports of allergic reactions following ingestion have been reported for the majority of natural color additives. It is concluded that the ingestion of natural color additives presents a very low risk of provoking adverse reactions.”

Advances In Food Nutrition Research • July 2001

The role of natural color additives in food allergy

Author information

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Abstract

A critical evaluation of the available information demonstrates that reactions to natural color additives are rare. Studies of turmeric and carotenoid pigments administered in mixtures with other food colorings failed to definitely identify reactions to either color additive. For carotenoids, the one case report of an adverse reaction was not conclusive. An anaphylactic reaction to saffron does suggest an IgE-mediated reaction, but the high use of saffron as compared with this single report of an adverse reaction suggests that sensitivity to saffron is extremely rare. Numerous reports of reactions to grapes or grape products have been reported in the literature, but no reports of sensitivities to grape skin extract or grape color extract were found. In rare cases, annatto dye may provoke a severe, adverse reaction in individuals with an uncommon hypersensitivity, and may aggravate the symptoms of patients suffering from recurrent urticaria. In its long history of use, there has been only one reported case of anaphylaxis resulting from the ingestion of annatto. Studies designed to investigate the role of annatto in recurrent urticaria sufferers were limited due to the absence of double-blind challenge and placebo controls. A number of cases of adverse reactions to carmine following ingestion have been reported in the literature. These adverse reactions suggest an IgE-mediated hypersensitivity. In many of the reported cases, the cause of sensitization to carmine was topical exposure from the use of carmine-containing cosmetics or occupational exposure to carmine and not from ingestion of carmine-containing foods and beverages. Following sensitization, affected individuals would be sensitive to carmine and the amounts present in foods and beverages could elicit allergic reactions. It is not known whether all individuals with carmine sensitivity induced through topical use are sensitive to the ingestion of carmine in foods. However, reactions to carmine solely because of ingestion are likely to be exceedingly rare due to the low use levels of carmine in foods and beverages. Despite their widespread use in food products, few reports of allergic reactions following ingestion have been reported for the majority of natural color additives. It is concluded that the ingestion of natural color additives presents a very low risk of provoking adverse reactions.

http://www.ncbi.nlm.nih.gov/pubmed/11285683

Asia Pacific Journal Of Clinical Nutrition • July 2001

Implications from and for food cultures for cardiovascular diseases: Japanese food, particularly Okinawan diets

Author information

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Abstract

Okinawans, who have a different ethnicity and food cultural history to other Japanese nationals, and an exceptional longevity have been studied at home and as migrant groups in Hawaii and Brazil. Biomarkers for fish and soy intake and intervention studies indicate that these foods, along with seaweed and green vegetables are candidates for chronic non-communicable disease prevention.

Full text, PDF with 7 references

http://apjcn.nhri.org.tw/server/APJCN/10/2/144.pdf

Critical Reviews In Biotechnology • January 2000

Lycopene in tomatoes: chemical and physical properties affected by food processing

Author information

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Abstract

Lycopene is the pigment principally responsible for the characteristic deep-red color of ripe tomato fruits and tomato products. It has attracted attention due to its biological and physicochemical properties, especially related to its effects as a natural antioxidant. Although it has no provitamin A activity, lycopene does exhibit a physical quenching rate constant with singlet oxygen almost twice as high as that of beta-carotene. This makes its presence in the diet of considerable interest. Increasing clinical evidence supports the role of lycopene as a micronutrient with important health benefits, because it appears to provide protection against a broad range of epithelial cancers. Tomatoes and related tomato products are the major source of lycopene compounds, and are also considered an important source of carotenoids in the human diet. Undesirable degradation of lycopene not only affects the sensory quality of the final products, but also the health benefit of tomato-based foods for the human body. Lycopene in fresh tomato fruits occurs essentially in the all-trans configuration. The main causes of tomato lycopene degradation during processing are isomerization and oxidation. Isomerization converts all-trans isomers to cis-isomers due to additional energy input and results in an unstable, energy-rich station. Determination of the degree of lycopene isomerization during processing would provide a measure of the potential health benefits of tomato-based foods. Thermal processing (bleaching, retorting, and freezing processes) generally cause some loss of lycopene in tomato-based foods. Heat induces isomerization of the all-trans to cis forms. The cis-isomers increase with temperature and processing time. In general, dehydrated and powdered tomatoes have poor lycopene stability unless carefully processed and promptly placed in a hermetically sealed and inert atmosphere for storage. A significant increase in the cis-isomers with a simultaneous decrease in the all-trans isomers can be observed in the dehydrated tomato samples using the different dehydration methods. Frozen foods and heat-sterilized foods exhibit excellent lycopene stability throughout their normal temperature storage shelf life. Lycopene bioavailability (absorption) can be influenced by many factors. The bioavailability of cis-isomers in food is higher than that of all-trans isomers. Lycopene bioavailability in processed tomato products is higher than in unprocessed fresh tomatoes. The composition and structure of the food also have an impact on the bioavailability of lycopene and may affect the release of lycopene from the tomato tissue matrix. Food processing may improve lycopene bioavailability by breaking down cell walls, which weakens the bonding forces between lycopene and tissue matrix, thus making lycopene more accessible and enhancing the cis-isomerization. More information on lycopene bioavailability, however, is needed. The pharmacokinetic properties of lycopene remain particularly poorly understood. Further research on the bioavalability, pharmacology, biochemistry, and physiology must be done to reveal the mechanism of lycopene in human diet, and the in vivo metabolism of lycopene. Consumer demand for healthy food products provides an opportunity to develop lycopene-rich food as new functional foods, as well as food-grade and pharmaceutical-grade lycopene as new nutraceutical products. An industrial scale, environmentally friendly lycopene extraction and purification procedure with minimal loss of bioactivities is highly desirable for the foods, feed, cosmetic, and pharmaceutical industries. High-quality lycopene products that meet food safety regulations will offer potential benefits to the food industry.

http://www.ncbi.nlm.nih.gov/pubmed/11192026

“Overall, the role of oxidative stress in disease, especially cancer and coronary heart disease, has probably been overstated; other components of the diet (other nutrients, phytochemicals and dietary fiber) likely play a significantly greater role.”

Nutrition Research • March 2000

Antioxidants and disease: More questions than answers

By Norman J. Temple, PhD

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Abstract

Reactive oxygen species are widely believed to be involved in the etiology of many diseases as indicated by the signs of oxidative stress seen in those diseases. Conversely, antioxidants are believed to be protective. An important part of the supporting evidence is the consistently-seen inverse association between, on the one hand, intake of ß-carotene and vitamin C and of fruit and vegetables, and, on the other hand, risk of cancer and coronary heart disease (CHD). However, the failure of supplemental ß-carotene to prevent these diseases in intervention trials suggests that the associations for that nutrient reflect confounding rather than cause and effect. With respect to other antioxidants there is inconsistent evidence that supplements of vitamin E may have some ability to prevent cancer and CHD while selenium may prevent cancer. Overall, the role of oxidative stress in disease, especially cancer and CHD, has probably been overstated; other components of the diet (other nutrients, phytochemicals and dietary fiber) likely play a significantly greater role. The possible benefits of supplements are discussed.

www.sciencedirect.com/science/article/pii/S027153170000138X

“In conclusion, an increased content of rapeseed oil in pig feed changes the fatty acid composition of the pig fat in a way that has a potential to reduce blood cholesterol concentrations in human subjects. However, intake of pig fat with a higher content of unsaturated fatty acids needs to be matched by a higher dietary intake of vitamin E.”

British Journal Of Nutrition • August 2000

Cholesterol-lowering potential in human subjects of fat from pigs fed rapeseed oil

Author information

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Abstract

The possibility of achieving blood-lipid-lowering characteristics of pig fat by increasing the content of unsaturated fat in pig feed was evaluated. Three pig feeding regimens were applied: basal feed (no added fat or vitamin E), basal feed + rapeseed oil (60 g/kg feed), and basal feed + rapeseed oil (60 g/kg) + vitamin E (200 mg/kg). Meat and meat products from the three pig groups were incorporated into diets providing 86 g pig fat/10 MJ. The diets were served to twelve healthy human male subjects for 3 weeks each in a randomised crossover design. The diets prepared from pigs fed rapeseed oil had a lower content of saturated fatty acids (approximately 9 v. 11% of energy) and a higher content of polyunsaturated fatty acids (approximately 6 v. 4% of energy) than the diet prepared from pigs fed the basal feed. Diets based on fat from pigs fed the rapeseed oil resulted in significantly lower (approximately 4%, P = 0.019) total serum cholesterol concentration compared with the diet from pigs fed the basal feed. No differences were observed in LDL-, HDL- or VLDL-cholesterol, or in triacylglycerol or VLDL-triacylglycerol concentrations. Addition of vitamin E to the pig feed resulted in only a minor increase in vitamin E content in the human subjects’ diet and the vitamin E content was low in all three pig diets. Plasma vitamin E concentration in the human subjects at the end of the period with diets from pigs fed rapeseed oil without vitamin E was significantly lower (P = 0.04) than in the other two diet periods. In conclusion, an increased content of rapeseed oil in pig feed changes the fatty acid composition of the pig fat in a way that has a potential to reduce blood cholesterol concentrations in human subjects. However, intake of pig fat with a higher content of unsaturated fatty acids needs to be matched by a higher dietary intake of vitamin E.

http://www.ncbi.nlm.nih.gov/pubmed/11029964

“There are pronounced differences in tissue carotenoid patterns, extending also to the distribution between the all-trans and various cis isomers of the respective carotenoids. Antioxidant functions are associated with lowering DNA damage, malignant transformation, and other parameters of cell damage in vitro as well as epidemiologically with lowered incidence of certain types of cancer and degenerative diseases, such as ischemic heart disease and cataract. They are of importance in the process of aging. Reactive oxygen species occur in tissues and cells and can damage DNA, proteins, carbohydrates, and lipids. These potentially deleterious reactions are controlled in part by antioxidants that eliminate prooxidants and scavenge free radicals ... The water-soluble antioxidant vitamin C can reduce tocopheroxyl radicals directly or indirectly and thus support the antioxidant activity of vitamin E ...”

Annals Of The New York Academy Of Sciences • September 1992

Antioxidant functions of vitamins
Vitamins E and C, beta-carotene, and other carotenoids

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Abstract

Tocopherols and tocotrienols (vitamin E) and ascorbic acid (vitamin C) as well as the carotenoids react with free radicals, notably peroxyl radicals, and with singlet molecular oxygen (1O2), this being the basis of their function as antioxidants. RRR-alpha-tocopherol is the major peroxyl radical scavenger in biological lipid phases such as membranes or low-density lipoproteins (LDL). L-Ascorbate is present in aqueous compartments (e.g. cytosol, plasma, and other body fluids) and can reduce the tocopheroxyl radical; it also has a number of metabolically important cofactor functions in enzyme reactions, notably hydroxylations. Upon oxidation, these micronutrients need to be regenerated in the biological setting, hence the need for further coupling to nonradical reducing systems such as glutathione/glutathione disulfide, dihydrolipoate/lipoate, or NADPH/NADP+ and NADH/NAD+. Carotenoids, notably beta-carotene and lycopene as well as oxycarotenoids (e.g. zeaxanthin and lutein), exert antioxidant functions in lipid phases by free-radical or 1O2 quenching. There are pronounced differences in tissue carotenoid patterns, extending also to the distribution between the all-trans and various cis isomers of the respective carotenoids. Antioxidant functions are associated with lowering DNA damage, malignant transformation, and other parameters of cell damage in vitro as well as epidemiologically with lowered incidence of certain types of cancer and degenerative diseases, such as ischemic heart disease and cataract. They are of importance in the process of aging. Reactive oxygen species occur in tissues and cells and can damage DNA, proteins, carbohydrates, and lipids. These potentially deleterious reactions are controlled in part by antioxidants that eliminate prooxidants and scavenge free radicals. Their ability as antioxidants to quench radicals and 1O2 may explain some anticancer properties of the carotenoids independent of their provitamin A activity, but other functions may play a role as well. Tocopherols are the most abundant and efficient scavengers of peroxyl radicals in biological membranes. The water-soluble antioxidant vitamin C can reduce tocopheroxyl radicals directly or indirectly and thus support the antioxidant activity of vitamin E; such functions can be performed also by other appropriate reducing compounds such as glutathione (GSH) or dihydrolipoate. The biological efficacy of the antioxidants is also determined by their biokinetics.

http://www.ncbi.nlm.nih.gov/pubmed/1444060

American Journal Of Clinical Nutrition • January 1991

Antioxidant defense systems: the role of carotenoids, tocopherols, and thiols

Author information

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Institut für Physiologische Chemie I, Universität Düsseldorf, FRG

Abstract

“Reactive oxygen species occur in tissues and can damage DNA, proteins, carbohydrates, and lipids. These potentially deleterious reactions are controlled by a system of enzymatic and nonenzymatic antioxidants which eliminate prooxidants and scavenge free radicals. The ability of the lipid-soluble carotenoids to quench singlet molecular oxygen may explain some anticancer properties of the carotenoids, independent of their provitamin A activity. Tocopherols are the most abundant and efficient scavengers of hydroperoxyl radicals in biological membranes. Water-soluble antioxidants include ascorbate and cellular thiols. Glutathione is an important substrate for enzymatic antioxidant functions and is capable of nonenzymatic radical scavenging. Thiols associated with membrane proteins may also be important to the antioxidant systems. Interactions between the thiols, tocopherols, and other compounds enhance the effectiveness of cellular antioxidant defense.”

http://www.ncbi.nlm.nih.gov/pubmed/1985387

“Protein digestibility may be reduced by the modification of the protein molecule (blocking of active amino acid side-chains, establishment of crosslinks) or by the formation of compounds that inhibit digestive enzymes. Biological value may be diminished by the loss of essential amino acids and/or their reduced specific availability. Figures for the reduction inavailable lysine (blocked lysine) in different milk products processed according to conventional procedures are given and discussed. More subtile effects of milk processing on milk digestibility and stomach emptying are mentioned.”

Journal Of Nutritional Science • Vitaminology (Tokyo) • 1990

Influence of processing on protein quality

By J Mauron
University of Fribourg, Switzerland

Abstract

In the first part the reactions and interactions of protein with macroconstituents of our food during processing are exposed from the chemical point of view. The reactions involving only protein (formation of isopeptides, of lysinoalanine, racemization) and the interactions with carbohydrates (Maillard reaction), oxidized lipids and polyphenols are briefly presented. Emphasis is put on the Maillard reaction since it is the most frequent reaction occurring during food processing and storage. The key compound rendering lysine unavailable in processed and stored foodstuffs in N epsilon-fructoselysine (FL). Its oxidative degradation product, N epsilon-carboxymethyllysine (CML) is found in variable but significant amounts in heat processed proteins. An interesting newer finding is that tryptophan can participate in a Maillard reaction with its indole-NH-group. In the second part an overview is given on the impact these reactions have on the two components of protein nutritive value, namely digestibility and biological value. Again, most examples will be related to the Maillard reaction. Protein digestibility may be reduced by the modification of the protein molecule (blocking of active amino acid side-chains, establishment of crosslinks) or by the formation of compounds that inhibit digestive enzymes. (Inhibition of aminopeptidase by an advanced Maillard derivative of lysine). Biological value may be diminished by the loss of essential amino acids and/or their reduced specific availability. Ion-exchange chromatography of the protein hydrolyzate is the method of choice to determine amino acid losses. It also provides some clues for the type of processing damage by the presence of unusual amino acids in the chromatogramme (e.g. furosine, lysinoalanine). Global amino acid bioavailability is defined. It is of a complex nature and can only be truely determined in a bioassay in the animal. Specific availability of an amino acid is linked to particular structural features. Thus, specific lysine availability is determined by the presence of a free or “reactive” epsilon-amino group. This is the basis for the analytical methods for available lysine. In the third part, the practical application of this knowledge to processed foods is shown using milk and vegetable protein as examples. Figures for the reduction in available lysine (blocked lysine) in different milk products processed according to conventional procedures are given and discussed. More subtile effects of milk processing on milk digestibility and stomach emptying are mentioned. The effects on protein nutritional value of extrusion-cooking of legume seeds and cereal flours are, then, presented. (ABSTRACT TRUNCATED AT 250 WORDS)

http://www.ncbi.nlm.nih.gov/pubmed/2081988

TOMATOES

According to the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration, fresh tomatoes fall into the 4.3-4.9 range when it comes to acidity. (pH is the most widely used scientific method for ranking acidity, and it goes from 0-14, with low numbers being the most acidic and high numbers being the least acidic.) For canned tomatoes and tomato paste, the pH range is 3.5-4.7. For tomato juice, the range is 4.1-4.6. Vegetables like celery, broccoli, carrots, romaine lettuce, and spinach typically have a higher (less acidic) pH range of 5-7, and fruits like apples, oranges, grapes, grapefruit, and blueberries typically have a range that include this 4-5 level but also dips down lower into the pH 3-4 range.

Canned tomatoes are typically more acidic than fresh tomatoes due to the impact of the canning process. The pH of canned tomatoes can dip down into the 3.5 pH range. For this reason, avoiding canned tomatoes would be another recommendation if a person were trying to consume foods with less acidity.

Is the acidity of tomatoes a bad thing? For individuals with healthy digestive function and no allergy to tomatoes, their degree of acidity might not be a bad thing after all. All of the World's Healthiest Foods have their own unique pH, and the pH of tomatoes is fully in keeping with the pH range that covers most fruits and vegetables.

There's another perspective, however, for addressing the issue of acidity in tomatoes. This perspective does not look at the question of acidity from a Western science standpoint but from the standpoint of other traditions involving whole body acid-base balance and its relationship to diet. In the case of these other traditions, including that of traditional Chinese medicine and the macrobiotic approach to diet, tomatoes are actually considered as the opposite of acidic.

In these traditions tomatoes are considered to be an alkalizing vegetable that will help lower the body's acidity when digested and metabolized. For example, it is the ability of tomatoes to help alkalize the blood that makes them recommended as a food that might help improve certain health problems that are understood as problems of excessive acidity. Because a slightly alkaline whole body balance is viewed as desirable in these traditions, tomatoes are included along with other alkalizing foods as those that are recommended to help restore this balance.

CHAPTER THIRTY

World Congress on Public Health and Nutrition March 10-12, 2016 Madrid, Spain

The Peer Review

World Congress on Public Health and Nutrition 2016 is organized by OMICS International and would be held during Mar 10 - 12, 2016 at Melia Avenida America Calle Juan Ignacio Luca de Tena, Madrid, Spain. Nutritionists, Dieticians, Health Promotion Practitioners, Physicians, Health Advocates, Nutrition, Epidemiologists, Nutrition Educators, Community Health Workers, Public Health Departments, Health Consumers, Health Policy Makers, Physician Assistants, Nurse Midwives, Nutrition Trainers, Nurse Practitioners, Students

The theme of the congress is "Integrated approaches for promoting Public Health through Nutrition" to provide a premier inter-multi-trans-disciplinary forum for researchers, practitioners and educators to present and discuss about the most recent innovations, trends, and concerns, practical challenges encountered and the solutions adopted in the health promotion, disease prevention, program development, and nutrition interventions.

In the light of this theme, the conference series aims at providing the links between diet and health by creating a platform for active participation, exchange of expertise and lateral thinking from health researchers, scientists, policy makers, practitioners and educators through invited plenary lectures, symposia, workshops, invited sessions and oral and poster sessions of unsolicited contributions.

World Congress on Public Health and Nutrition

Food Addiction and the Controversial Results of the Food-Tax

March 10-12, 2016 Madrid, Spain

Umberto Pagano
University Magna Graecia of Catanzaro, Italy

Abstract

The global food scenario has changed a lot in recent years. The food industry, in fact, develops ceaselessly formulas to increase the organoleptic attractiveness of the foods and their compulsive consumption. These are known as “hyperpalatable foods”, generally obtained through sophisticated processes (“highly processed food”) and containing abnormal amounts of sugar, fat and salt (in full: “junk food”). These foods are supposed to be one of the reason of widespreading food-addiction, not to mention the pervasive obesity epidemic. The paper proposes, in its first part, a phenomenology of food addiction, and then tackles the topic of controversial “food taxes” (tax on foods with contents of fat, sugar, salt above certain thresholds), recently applied in several European countries (Denmark, Finland, France, Hungary), in order to cope with alarming phenomena of obesity, overweight and compulsive consumption of junk food. Over the past 15 years, the debate over them is greatly animated, creating sometimes opposing barricades. The issues - ethical, legal and technical - related to the implementation of a food-tax are numerous and thorny, not to mention the fact that the effectiveness of such a policy is still far to be proved. Empirical data show fairly limited results of food-tax policies to date. The paper, through a comprehensive analysis of data and literature available, outlines the key socio-economic reasons for this failure and possible corrections to be made. Key-words: Food-addiction, health-policies, food-tax, hyper-palatable, highly-processed food.

PDF, second article:

http://www.omicsonline.org/2161-0711/2161-0711.C1.019_036.pdf

World Congress on Public Health and Nutrition

Fast food consumption among university students, Saudi Arabia – A cross-sectional study (2014)

Yasser Fahd Al Towyan
Majmaah University, Saudi Arabia

Abstract

Background: Fast food consumption (FFC) is one of the most common eating habits now-a-days with escalated prevalence in the recent decades. It is a risk factor for development of many diseases, and the risk increases with increase FFC. Objectives: The study aimed to find the prevalence of FFC among the university students, to identify factors that contribute to the FFC among them, and to test student's level of awareness regarding the health issues occur due to the consumption of fast food. Methods: This cross sectional study was conducted from December 2013 - May 2014. The target population was students of either gender studying in Majmaah University. A total of 505 students (325) males and (180) females aged between 18-26 years were randomly chosen from Colleges of Majmaah University. Results: Two hundred and ten (41.6%) of the participants (159 males, 51 females) choose fast food as their usual meal. Fast food as a usual meal was consumed more by male students as compared to female students ($p<0.001$). Female students were attracted by taste more than male students, female students were attracted to advertisements more than male students ($p<0.001$). Consuming fast food in students who stay away from the family was significantly more in male students as compared to female students ($p<0.001$). Conclusion: The prevalence of FFC among Majmaah University students is very high. More than one quarter of the participants were consuming fast food daily which itself is alarming. Some intervention/awareness programmes should be conducted to minimize the harmful effects of FFC.

Yasser Fahd ALTowyan is a 6th year Medical Student at Majmaah University, Saudi Arabia. He has presented his researsh at two regional conferences and published in local medical journals. Currently, he is planning to do more research regarding national health and quality of life style.

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http://www.omicsonline.org/2161-0711/2161-0711.C1.019_014.pdf

World Congress on Public Health and Nutrition

Attitudes of college students regarding food additives

Mustafa Ozgur and Asli Ayar Ucar
Ankara University, Turkey

Abstract

In this study, it was aimed to determine university students' attitudes towards food addititives. This study was made on randomly selected 450 voluteered students studying in the faculties of Ankara University (Faculty of Pharmacy, Political Sciences and Science). Data were collected with questionnaire. The questionnaire comprised general information and questions to determine, students' attitudes about food additives. The data obtained from the survey results were analyzed using SPSS software. 46.0% of students were male while 54.0% of female. The mean age of students was 21.7±2.05 years. Considering of students' concerns about the use of food additives, the majority of students (43.3%) thought that food additives were harmful effect on health. In the use of food additives in order to use visual deception were those who thought that it was 16%. It was found that 40.9% of students thought that legal control of food additives was not enough and 40.2% thought that they can cause cancer, 36.9% of students thought that if food addititives weren't used, foods will be healthier. The majority of (49.6%) students thought that food addititives was not used in accordance to the law. According to the results, it can be said that students has negative attitudes towards food additives. It is great that food additives has a role of nutritional requirments of the growing world population when properly used. It was concluded that students need more information about food addititives and at the same time nutrition education should be given in all sections for longer periods.

Mustafa Ozgur graduated from Erciyes University in 2014 and is a Research Assistant in Nutrition and Dietetics Departmant of Ankara University. At same time, he is doing his Master's in Nutrition and Dietetics.
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http://www.omicsonline.org/2161-0711/2161-0711.C1.019_009.pdf

World Congress on Public Health and Nutrition

Safeguarding of food quality using nanoscalled containers immobilized on active packaging

Svetlana Stolarov, Ionel Adrian Dinu, Wolfgang Meier and Cornelia Palivan
University of Basel, Switzerland

Abstract

The interest to apply nanotechnology in food preservation and in food quality control largely increased in last few years. The development of active packaging materials which are able to interact with substances produced during the food decay and preserve the quality by releasing the active compounds or to sense its decay at the early stage, is very important issue to be address .[1, 2] The aim of our project is to develop the method for long-term immobilization of nanoscaled containers such as polymer vesicles (polymersomes) on the solid support. The active compounds are stored in polymer vesicles attached to the packaging surface and are released into the food upon first signs of decline in the freshness of the food. The polymersomes, formed by the self-assembly of amphiphilic block copolymers, were covalently attached via hydrazone bonds on the glass surface. Since, the prerequisite of such systems is to fulfil healthy and safety issues, a high stability of the attached nanocontainers is required. The architecture and stability of attached vesicles were not affected for more than 11 months under dry conditions. The glass surfaces before and after vesicle attachment were characterized by contact angle, AFM and QCM techniques. The stability of active surfaces under wet conditions and various pH media, as well as the immobilization on other surfaces, is still under investigation.

Svetlana Stolarov has completed her Master degree in chemistry at University of Basel in 2013. Currently she is a PhD student in Prof. Cornelia Palivans group at University of Basel.
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http://www.omicsonline.org/2161-0711/2161-0711.C1.018_024.pdf

World Congress on Public Health and Nutrition
March 10-12, 2016 Madrid, Spain

Acrylamide in foods: A review and recent updates

Huseyin Ayvaz
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Abstract

Acrylamide is a chemical compound naturally formed during processes such as frying, roasting and baking in a wide variety of foods including French fries, potato chips, cereal, bread and coffee and it has been reported to be a human neurotoxin, a rodent carcinogen and a “probable carcinogen to humans”. Maillard reaction between sugars and amino acids is considered to be the main mechanism for acrylamide formation, with asparagine and reducing sugars as the major reactants present in foods. It has been found to cause cancer in laboratory animals when consumed in excessive amounts (LD50 values are in the range of 107-203 mg/kg bw in rats). Acrylamide has the ability to be absorbed by the skin, inhaled by mucosa or by ingestion through the oral route. Upon consumption through the diet, acrylamide is quickly absorbed from gastrointestinal tract and distributed to the tissues. Acrylamide is metabolized to glycidamide in the liver and becomes more reactive towards DNA and proteins. Up to 50 % of the acrylamide obtained from diet in pregnant woman can be transferred to the fetus via blood through the placenta. As of now, the greatest risk from acrylamide seems to be the neurotoxic effects in humans due to the changes that occur in the central nervous system after exposure to high doses of acrylamide. This study aims to review the precursors of acrylamide, how it is formed in foods, possible mitigating strategies and analytical methods available for its measurement emphasizing some recent infrared-based methods developed for its measurement in our laboratory.

Huseyin Ayvaz completed his master and PhD at the Ohio State University, Columbus, OH and he currently works for Canakkale Onsekiz Mart University, Department of Food Engineering, in Turkey. His research involves the use of infrared spectroscopy combined with chemometrics in food and agricultural products with emphasizes given on handheld and portable infrared spectrometers.

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http://www.omicsonline.org/2161-0711/2161-0711.C1.018_011.pdf

World Congress on Public Health and Nutrition
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The use of liquid smoke condensate in foods and its effect on health

Zayde Ayvaz and Hasan Huseyin Atar
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Abstract

Traditional smoking application using the smoke produced by burning woods has been utilized as a preservation technique for centuries. However, wood smoke generates some unfavorable compounds such as Polycyclic Aromatic Hydrocarbons (PAHs) upon pyrolysis, which occurs between 180 and 350 °C. These PAHs are generally known to be carcinogenic even though some of the PAHs are not actually considered as carcinogenic themselves but believed to be served as precursors. Benzo(a)pyrene, one of the important compounds listed among the PAHs, has been shown to cause birth defects when its concentration in foods exceeds 300 ppm. This fact brought some restrictions to PAH presence in commercially available smoked products in some countries including the European Union countries and the United States. The strictest restriction is applied within the European Union with 0.002 ppm allowance. On the other hand, smoke condensates have been used in food industry over three decades. Once water and wood smoke evaporates and goes through some separation and filtration steps, so called “liquid smoke condensate” is obtained. The preparation steps used during the production of liquid smoke condensate help avoiding tar and unfavorable compounds like PAHs. Recent studies have elucidated that liquid smoke foods has either no or trace amount of Benzo(a)pyrene present. This study aims to review the importance of using liquid smoke condensates in food products from health perspective as a replacement to traditional smoking due to the negative health implications of PAH containing traditionally smoked foods.

Zayde Ayvaz completed her PhD in Ankara University, Turkey and additional postdoctoral study in The University of Auckland, New Zealand. She received Associate Professor degree at the age of 29. She has published more than 30 papers in peer-reviewed journals and has been serving as an editorial board member on more than 25 scientific journals. She currently works for Canakkale Onsekiz Mart University, Department of Marine Technology Eng. located in Turkey.

http://www.omicsonline.org/2161-0711/2161-0711.C1.018_008.pdf

CHAPTER THIRTY-ONE

Tap Water Additives

The Peer Review

What's in Your Drinking Water?

Many prominent scientists are alarmed by the content of some drinking water and actively seek to change the processes involved. The practice of making water safe to drink actually involves adding large amounts of extremely poisonous chemicals to it. Key scientists are now providing evidence that long-term ingestion of small amounts of chemicals like these could be the cause of some major health problems.

Here is a list of just a few of the chemicals routinely added to our water supply:

- Liquified chlorine
- Fluorosilicic acid
- Aluminium sulphate
- Calcium hydroxide
- Sodium silicofluoride

Even if the water leaves the source in a relatively clean state, don't forget that your water travels through pipes, which may have been underground since Victorian times. It is almost impossible for the water not to become contaminated by something undesirable.

Contaminants in Tap Water

Tap water is treated with a large number of chemicals in order to kill bacteria and other microorganisms. In addition, it may contain other undesirable contaminants like toxic metal salts, hormones and pesticides, or it may become contaminated by chemicals or microbes within pipes (e.g. lead, bacteria, protozoa).

Typical Tap Water Content:

- Chlorine
- Fluorine compounds
- Trihalomethanes (THMs)
- Salts of:
  - arsenic
  - radium
  - aluminium
  - copper
  - lead
  - mercury
  - cadmium
  - barium
- Hormones
- Nitrates
- Pesticides

Testing Your Own Water

You can assess the quality of your water by testing for Total Dissolved Solids (TDS) with a TDS meter which reads the TDS instantly and gives a read-out in parts per million (ppm) TDS. Generally, water with a TDS of 500 ppm or more is regarded as unfit for consumption. Most tap water ranges from 150 to 420 ppm TDS. A Reverse Osmosis system typically produces water with a TDS of 90 - 95% of the incoming water.

Fluoride In Water

Another very important health hazard is fluoride, which is added by some water authorities in the US. About 60% of the US water supply is fluoridated despite a huge body of scientific evidence in opposition. It's also present in many toothpastes and mouthwashes, in the air we breathe and the dirt and dust our children play in.

Fluoridation of water is banned in all European countries except for the UK where about 10% is Fluoridated.

Dr. Hardy Limeback, Head of the Department of Preventative Dentistry for the University of Toronto and President of the Canadian Association for Dental Research. Dr. Limeback is Canada's leading fluoride authority and, until recently, the country's primary promoter of the controversial additive. As stated by UK health researcher and author, Phillip Day, fluoridation of the public water system is a case of mass medication without consent. Dr. Limeback recently publicly apologized for pushing fluoridation. So what's in your water? Let's look ...

“The rank order in decreasing genotoxicity was as follows: MX > DBN > IA > BCN > BA > TCN > DBA > DCA > CA, TCA, DCN > CN, CH. MX was approximately 370,000 times more genotoxic than DCA. In the microplate-based cytotoxicity assay, cytotoxic potencies of the 13 DBPs were compared and ranked in decreasing order as follows: MX > IA > DBN > BCN > BA > TCN > DCN > CA > DCA > DBA > CN > TCA > CH. MX was approximately 19,200 times more cytotoxic than CH. A statistically significant correlation was found between cytotoxicity and genotoxicity of the 13 DBPs in S. typhimurium.”

Mutagenesis • January 2016

Comparative cytotoxic and genotoxic potential of 13 drinking water disinfection by-products using a microplate-based cytotoxicity assay and a developed SOS/umu assay

Author information

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Abstract

The implications of disinfection by-products (DBPs) present in drinking water are of public health concern because of their potential mutagenic, carcinogenic and other toxic effects on humans. In this study, we selected 13 main DBPs found in drinking water to quantitatively analyse their cytotoxicity and genotoxicity using a microplate-based cytotoxicity assay and a developed SOS/umu assay in Salmonella typhimurium TA1535/pSK1002. With the developed SOS/umu test, eight DBPs: 3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]-fura3-chloro-4-(dichloromethyl)-5-hydroxy-2-[5H]-furanone (MX), dibromoacetonitrile (DBN), iodoacetic acid (IA), bromochloroacetonitrile (BCN), bromoacetic acid (BA), trichloroacetonitrile (TCN), dibromoacetic acid (DBA) and dichloroacetic acid (DCA) were significantly genotoxic to S. typhimurium. Three DBPs: chloroacetic acid (CA), trichloroacetic acid (TCA) and dichloroacetonitrile (DCN) were weakly genotoxic, whereas the remaining DBPs: chloroacetonitrile (CN) and chloral hydrate (CH) were negative. The rank order in decreasing genotoxicity was as follows: MX > DBN > IA > BCN > BA > TCN > DBA > DCA > CA, TCA, DCN > CN, CH. MX was approximately 370 000 times more genotoxic than DCA. In the microplate-based cytotoxicity assay, cytotoxic potencies of the 13 DBPs were compared and ranked in decreasing order as follows: MX > IA > DBN > BCN > BA > TCN > DCN > CA > DCA > DBA > CN > TCA > CH. MX was approximately 19 200 times more cytotoxic than CH. A statistically significant correlation was found between cytotoxicity and genotoxicity of the 13 DBPs in S. typhimurium. Results suggest that microplate-based cytotoxicity assay and the developed SOS/umu assay are feasible tools for analysing the cytotoxicity and genotoxicity of DBPs, particularly for comparing their toxic intensities quantitatively.

http://www.ncbi.nlm.nih.gov/pubmed/26188195

“Two major classes of disinfection by-products are found in finished drinking water: haloacetic acids and trihalomethanes. Previously the haloacetic acids were shown to be cytotoxic, genotoxic, mutagenic, teratogenic and carcinogenic.”

Mutation Research • December 2014

Effect of drinking water disinfection by-products in human peripheral blood lymphocytes and sperm

Author information

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Abstract

BACKGROUND

Drinking water disinfection by-products (DBPs) are generated by the chemical disinfection of water and may pose hazards to public health. Two major classes of DBPs are found in finished drinking water: haloacetic acids (HAAs) and trihalomethanes (THMs). HAAs are formed following disinfection with chlorine, which reacts with iodide and bromide in the water. Previously the HAAs were shown to be cytotoxic, genotoxic, mutagenic, teratogenic and carcinogenic.

OBJECTIVES

To determine the effect of HAAs in human somatic and germ cells and whether oxidative stress is involved in genotoxic action. In the present study both somatic and germ cells have been examined as peripheral blood lymphocytes and sperm.

METHODS

The effects of three HAA compounds: iodoacetic acid (IAA), bromoacetic acid (BAA) and chloroacetic acid (CAA) were investigated. After determining appropriate concentration responses, oxygen radical involvement with the antioxidants, butylated hydroxanisole (BHA) and the enzyme catalase, were investigated in the single cell gel electrophoresis (Comet) assay under alkaline conditions, >pH 13 and the micronucleus assay.

RESULTS

In the Comet assay, BHA and catalase were able to reduce DNA damage in each cell type compared to HAA alone. In the micronucleus assay, micronuclei (MNi) were found in peripheral lymphocytes exposed to all three HAAs and catalase and BHA were in general, able to reduce MNi induction, suggesting oxygen radicals play a role in both assays.

CONCLUSION

These observations are of concern to public health since both human somatic and germ cells show similar genotoxic responses.

http://www.ncbi.nlm.nih.gov/pubmed/25771880

Mutation Research • January 2012

Comparison of DNA damage in human-derived hepatoma line (HepG2) exposed to the fifteen drinking water disinfection byproducts using the single cell gel electrophoresis assay

Author information

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Abstract

Disinfection of drinking water reduces pathogenic infection, but generates disinfection by-products (DBPs) in drinking water. In this study, the effect of fifteen DBPs on DNA damage in human-derived hepatoma line (HepG2) was investigated by the single cell gel electrophoresis (SCGE) assay. These fifteen DBPs are: four trihalomethanes (THMs), six haloacetic acides (HAAs), three haloacetonitriles (HANs), 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), and chloral hydrate (CH). Based on the minimal effective concentration (MEC) at which DBPs induced significant increase in olive tail moment (OTM), the rank order of DNA-damaging potency is: bromodichloromethane (BDCM)>dibromochlorom ethane (DBCM)>tribromomethane (TBM)>trichloromethane (TCM) of the four THMs; iodoacetic acid (IA)>bromoacetic acid (BA)>dibromoacetic acid (DBA)>dichloracetic acid (DCA)>trichloroacetic acid (TCA) of the five HAAs; dibromoacetonitrile (DBN)approximately dichloroacetonitrile (DCN)>trichlo roacetonitrile (TCN) of the three HANs. The DNA damaging potency of MX and CH is similar to TCA and DCA, respectively. IA is the most genotoxic DBP in the fifteen DBPs, followed by BA. Chloroacetic acid (CA) is not genotoxic in this assay. Our findings indicated that HepG2/SCGE is a sensitive tool to evaluate the genotoxicity of DBPs and iodinated DBPs are more genotoxic than brominated DBPs, but chlorinated DBPs are less genotoxic than brominated DBPs.

http://www.ncbi.nlm.nih.gov/pubmed/22108252

“the rank order of DNA-damaging potency is

[of unfilterable tap water disinfection by-products]:

bromodichloromethane (BDCM)>
dibromochloromethane (DBCM)>
tribromomethane (TBM)>
trichloromethane (TCM)
of the four trihalomethanes ;
iodoacetic acid (IA)>
bromoacetic acid (BA)>
dibromoacetic acid (DBA)>
dichloracetic acid (DCA)>
trichloroacetic acid (TCA)
of the five haloacetic acides;
dibromoacetonitrile (DBN)>
approximately dichloroacetonitrile (DCN)>
trichloroacetonitrile (TCN)
of the three haloacetonitriles.”

“Drinking water disinfectants react with natural organic material (NOM) present in source waters used for drinking water to produce a wide variety of by-products. Several hundred disinfections by-products (DBPs) have been identified, but none have been identified with sufficient carcinogenic potency to account for the cancer risks projected from epidemiological studies.”

Toxicology • August 2011

Potential carcinogenic hazards of non-regulated disinfection by-products: haloquinones, halo-cyclopentene and cyclohexene derivatives, N-halamines, halonitriles, and heterocyclic amines

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Abstract

Drinking water disinfectants react with natural organic material (NOM) present in source waters used for drinking water to produce a wide variety of by-products. Several hundred disinfections by-products (DBPs) have been identified, but none have been identified with sufficient carcinogenic potency to account for the cancer risks projected from epidemiological studies. In a search for DBPs that might fill this risk gap, the present study projected reactions of chlorine and chloramine that could occur with substructures present in NOM to produce novel by-products. A review of toxicological data on related compounds, supplemented by use of a quantitative structure toxicity relationship (QSTR) program TOPKAT®) identified chemicals with a high probability of being chronically toxic and/or carcinogenic among 489 established and novel DBPs. Classes of DBPs that were specifically examined were haloquinones (HQs), related halo-cyclopentene and cyclohexene (HCP&H) derivatives, halonitriles (HNs), organic N-chloramines (NCls), haloacetamides (HAMs), and nitrosamines (NAs). A review of toxicological data available for quinones suggested that HQs and HCP&H derivatives appeared likely to be of health concern and were predicted to have chronic lowest observed adverse effect levels (LOAELs) in the low µg/kg day range. Several HQs were predicted to be carcinogenic. Some have now been identified in drinking water. The broader class of HNs was explored by considering current toxicological data on haloacetonitriles and extending this to halopropionitriles. 2,2-dichloropropionitrile has been identified in drinking water at low concentrations, as well as the more widely recognized haloacetonitriles. The occurrence of HAMs has been previously documented. The very limited toxicological data on HAMs suggests that this class would have toxicological potencies similar to the dihaloacetic acids. Organic N-halamines are also known to be produced in drinking water treatment and have biological properties of concern, but no member has ever been characterized toxicologically beyond bacterial or in vitro studies of genotoxicity. The documented formation of several nitrosamines from secondary amines from both natural and industrial sources prompted exploration of the formation of additional nitrosamines. N-diphenylnitrosamine was identified in drinking waters. Of more interest, however, was the formation of phenazine (and subsequently N-chorophenazine) in a competing reaction. These are the first heterocyclic amines that have been identified as chlorination by-products. Consideration of the amounts detected of members of these by-product classes and their probable toxicological potency suggest a prioritization for obtaining more detailed toxicological data of HQs>HCP&H derivatives>NCls>HNs. Based upon a ubiquitous occurrence and virtual lack of in vivo toxicological data, NCls are the most difficult group to assign a priority as potential carcinogenic risks. This analysis indicates that research on the general problem of DBPs requires a more systematic approach than has been pursued in the past. Utilization of predictive chemical tools to guide further research can help bring resolution to the DBP issue by identifying likely DBPs with high toxicological potency.

http://www.ncbi.nlm.nih.gov/pubmed/21605618

“The use of alternative disinfectants other than chlorine generates new Disinfection By Products and alters their distribution. Systematic, comparative, in vitro toxicological data provides the water supply community with information to consider when employing alternatives to chlorine disinfection.”

Environmental And Molecular Mutagenesis • October 2010

Mammalian cell cytotoxicity and genotoxicity of the haloacetic acids, a major class of drinking water disinfection by-products

Author information

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http://www.ncbi.nlm.nih.gov/pubmed/20839218

Abstract

The haloacetic acids (HAAs) are disinfection by-products (DBPs) that are formed during the disinfection of drinking water, wastewaters and recreational pool waters. Currently, five HAAs [bromoacetic acid (BAA), dibromoacetic acid (DBAA), chloroacetic acid (CAA), dichloroacetic acid (DCAA), and trichloroacetic acid (TCAA); designated as HAA5] are regulated by the U.S. EPA, at a maximum contaminant level of 60 µg/L for the sum of BAA, DBAA, CAA, DCAA, and TCAA. We present a comparative systematic analysis of chronic cytotoxicity and acute genomic DNA damaging capacity of 12 individual HAAs in mammalian cells. In addition to the HAA5, we analyzed iodoacetic acid (IAA), diiodoacetic acid (DiAA), bromoiodoacetic acid (BIAA), tribromoacetic acid (TBAA), chlorodibromoacetic acid (CDBAA), bromodichloroacetic acid (BDCAA), and bromochloroacetic acid (BCAA). Their rank order of chronic cytotoxicity in Chinese hamster ovary cells was IAA > BAA > TBAA > CDBAA > DIAA > DBAA > BDCAA > BCAA > CAA > BIAA > TCAA > DCAA. The rank order for genotoxicity was IAA > BAA > CAA > DBAA > DIAA > TBAA > BCAA > BIAA > CDBAA. DCAA, TCAA, and BDCAA were not genotoxic. The trend for both cytotoxicity and genotoxicity is iodinated HAAs > brominated HAAs > chlorinated HAAs. The use of alternative disinfectants other than chlorine generates new DBPs and alters their distribution. Systematic, comparative, in vitro toxicological data provides the water supply community with information to consider when employing alternatives to chlorine disinfection. In addition, these data aid in prioritizing DBPs and their related compounds for future in vivo toxicological studies and risk assessment.

Abstract

“An occurrence study was conducted to measure five iodo-acids (iodoacetic acid, bromoiodoacetic acid, (Z)-3-bromo-3-iodo-propenoic acid, (E)-3-bromo-3-iodo-propenoic acid, and (E)-2-iodo-3-methylbutenedioic acid) and two iodo-trihalomethanes (iodo-THMs), (dichloroiodomethane and bromochloroiodomethane) in chloraminated and chlorinated drinking waters from 23 cities in the United States and Canada. Since iodoacetic acid was previously found to be genotoxic in mammalian cells, the iodo-acids and iodo-THMs were analyzed for toxicity. A gas chromatography (GC)/negative chemical ionization-mass spectrometry (MS) method was developed to measure the iodo-acids; iodo-THMs were measured using GC/high resolution electron ionization-MS with isotope dilution. The iodo-acids and iodo-THMs were found in waters from most plants, at maximum levels of 1.7 microg/L (iodoacetic acid), 1.4 microg/L (bromoiodoacetic acid), 0.50 microg/L ((Z)-3-bromo-3-iodopropenoic acid), 0.28 microg/L ((E)-3-bromo-3-iodopropenoic acid), 0.58 microg/L ((E)-2-iodo-3-methylbutenedioic acid), 10.2 microg/L (bromochloroiodomethane), and 7.9 microg/L (dichloroiodomethane). Iodo-acids and iodo-THMs were highest at plants with short free chlorine contact times (< 1 min), and were lowest at a chlorine-only plant or at plants with long free chlorine contact times (> 45 min). Iodide levels in source waters ranged from 0.4 to 104.2 microg/L (when detected), but there was not a consistent correlation between bromide and iodide. The rank order for mammalian cell chronic cytotoxicity of the compounds measured in this study, plus other iodinated compounds, was iodoacetic acid > (E)-3-bromo-2-iodopropenoic acid > iodoform > (E)-3-bromo-3-iodo-propenoic acid > (Z)-3-bromo-3-iodo-propenoic acid > diiodoacetic acid > bromoiodoacetic acid > (E)-2-iodo-3-methylbutenedioic acid > bromodiiodomethane > dibromoiodomethane > bromochloroiodomethane approximately chlorodiiodomethane > dichloroiodomethane. With the exception of iodoform, the iodo-THMs were much less cytotoxic than the iodo-acids. Of the 13 compounds analyzed, 7 were genotoxic; their rank order was iodoacetic acid >> diiodoacetic acid > chlorodiiodomethane > bromoiodoacetic acid > E-2-iodo-3-methylbutenedioic acid > (E)-3-bromo-3-iodo-propenoic acid > (E)-3-bromo-2-iodopropenoic acid. In general, compounds that contain an iodo-group have enhanced mammalian cell cytotoxicity and genotoxicity as compared to their brominated and chlorinated analogues.”

Environmental Science And Technology • November 2008

Occurrence and mammalian cell toxicity of iodinated disinfection byproducts in drinking water

Author information

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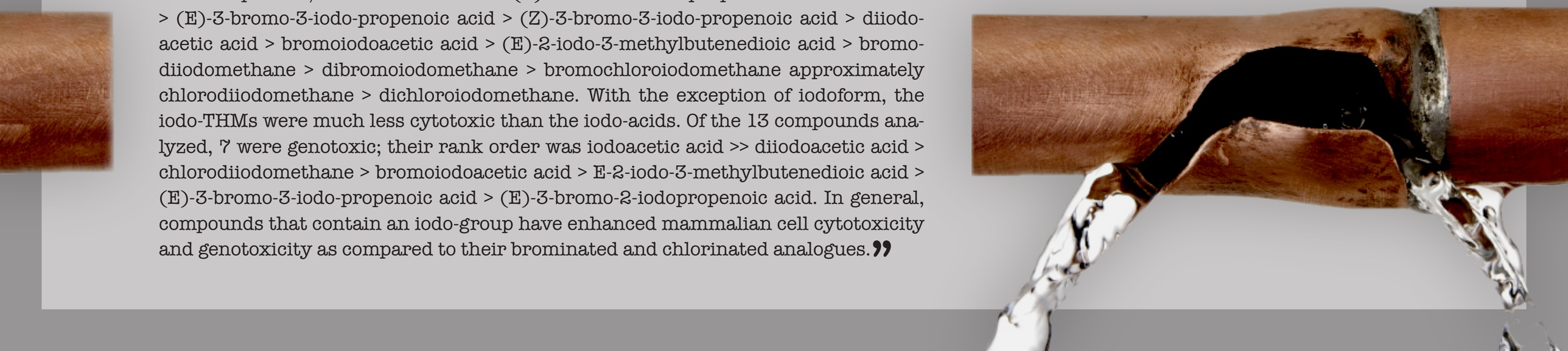

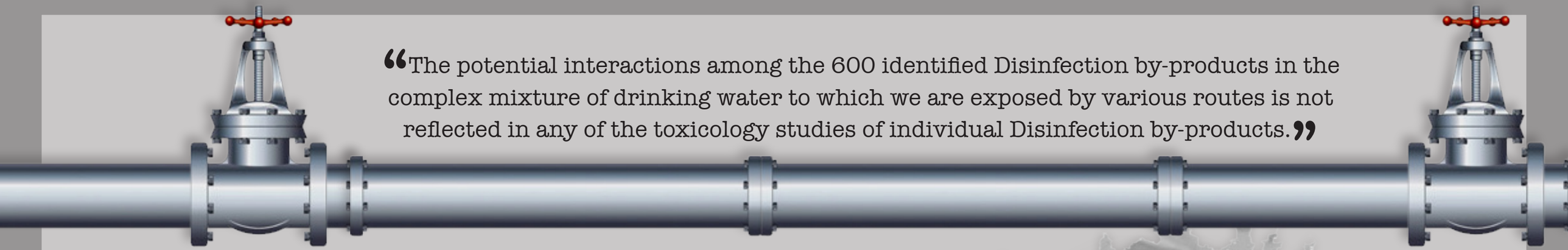

> “The potential interactions among the 600 identified Disinfection by-products in the complex mixture of drinking water to which we are exposed by various routes is not reflected in any of the toxicology studies of individual Disinfection by-products.”

Abstract

Disinfection by-products (DBPs) are formed when disinfectants (chlorine, ozone, chlorine dioxide, or chloramines) react with naturally occurring organic matter, anthropogenic contaminants, bromide, and iodide during the production of drinking water. Here we review 30 years of research on the occurrence, genotoxicity, and carcinogenicity of 85 DBPs, 11 of which are currently regulated by the U.S., and 74 of which are considered emerging DBPs due to their moderate occurrence levels and/or toxicological properties. These 74 include halonitromethanes, iodo-acids and other unregulated halo-acids, iodo-trihalomethanes (THMs), and other unregulated halomethanes, halofuranones (MX [3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone] and brominated MX DBPs), haloamides, haloacetonitriles, tribromopyrrole, aldehydes, and N-nitrosodimethylamine (NDMA) and other nitrosamines. Alternative disinfection practices result in drinking water from which extracted organic material is less mutagenic than extracts of chlorinated water. However, the levels of many emerging DBPs are increased by alternative disinfectants (primarily ozone or chloramines) compared to chlorination, and many emerging DBPs are more genotoxic than some of the regulated DBPs. Our analysis identified three categories of DBPs of particular interest. Category 1 contains eight DBPs with some or all of the toxicologic characteristics of human carcinogens: four regulated (bromodichloromethane, dichloroacetic acid, dibromoacetic acid, and bromate) and four unregulated DBPs (formaldehyde, acetaldehyde, MX, and NDMA). Categories 2 and 3 contain 43 emerging DBPs that are present at moderate levels (sub- to low-mug/L): category 2 contains 29 of these that are genotoxic (including chloral hydrate and chloroacetaldehyde, which are also a rodent carcinogens); category 3 contains the remaining 14 for which little or no toxicological data are available. In general, the brominated DBPs are both more genotoxic and carcinogenic than are chlorinated compounds, and iodinated DBPs were the most genotoxic of all but have not been tested for carcinogenicity. There were toxicological data gaps for even some of the 11 regulated DBPs, as well as for most of the 74 emerging DBPs. A systematic assessment of DBPs for genotoxicity has been performed for approximately 60 DBPs for DNA damage in mammalian cells and 16 for mutagenicity in Salmonella. A recent epidemiologic study found that much of the risk for bladder cancer associated with drinking water was associated with three factors: THM levels, showering/bathing/swimming (i.e., dermal/inhalation exposure), and genotype (having the GSTT1-1 gene). This finding, along with mechanistic studies, highlights the emerging importance of dermal/inhalation exposure to the THMs, or possibly other DBPs, and the role of genotype for risk for drinking-water-associated bladder cancer. More than 50% of the total organic halogen (TOX) formed by chlorination and more than 50% of the assimilable organic carbon (AOC) formed by ozonation has not been identified chemically. The potential interactions among the 600 identified DBPs in the complex mixture of drinking water to which we are exposed by various routes is not reflected in any of the toxicology studies of individual DBPs. The categories of DBPs described here, the identified data gaps, and the emerging role of dermal/inhalation exposure provide guidance for drinking water and public health research.

Mutation Research • November 2007

Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: a review and roadmap for research

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http://www.ncbi.nlm.nih.gov/pubmed/17980649

“A survey of disinfection byproduct (DBP) occurrence in the United States was conducted at 12 drinking water treatment plants. In addition to currently regulated disinfection byproducts, more than 50 disinfection byproducts that rated a high priority for potential toxicity were studied. In addition, 28 new, previously unidentified disinfection byproductss were detected. These included brominated and iodinated haloacids, a brominated ketone, and chlorinated and iodinated aldehydes.”

Environmental Science And Technology • December 2006

Occurrence of a new generation of disinfection byproducts

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Abstract

A survey of disinfection byproduct (DBP) occurrence in the United States was conducted at 12 drinking water treatment plants. In addition to currently regulated DBPs, more than 50 DBPs that rated a high priority for potential toxicity were studied. These priority DBPs included iodinated trihalomethanes (THMs), other halomethanes, a nonregulated haloacid, haloacetonitriles, haloketones, halonitromethanes, haloaldehydes, halogenated furanones, haloamides, and nonhalogenated carbonyls. The purpose of this study was to obtain quantitative occurrence information for new DBPs (beyond those currently regulated and/or studied) for prioritizing future health effects studies. An effort was made to select plants treating water that was high in total organic carbon and/or bromide to enable the detection of priority DBPs that contained bromine and/or iodine. THMs and haloacetic acids (HAAs) represented the two major classes of halogenated DBPs formed on a weight basis. Haloacetaldehydes represented the third major class formed in many of the waters. In addition to obtaining quantitative occurrence data, important new information was discovered or confirmed at full-scale plants on the formation and control of DBPs with alternative disinfectants to chlorine. Although the use of alternative disinfectants (ozone, chlorine dioxide, and chloramines) minimized the formation of the four regulated THMs, trihalogenated HAAs, and total organic halogen (TOX), several priority DBPs were formed at higher levels with the alternative disinfectants as compared with chlorine. For example, the highest levels of iodinated THMs-which are not part of the four regulated THMs-were found at a plant that used chloramination with no prechlorination. The highest concentration of dichloroacetaldehyde was at a plant that used chloramines and ozone; however, this disinfection scheme reduced the formation of trichloroacetaldehyde. Preozonation was found to increase the formation of trihalonitromethanes. In addition to the chlorinated furanones that have been measured previously, brominated furanones-which have seldom been analyzed-were detected, especially in high-bromide waters. The presence of bromide resulted in a shift to the formation of other bromine-containing DBPs not normally measured (e.g., brominated ketones, acetaldehydes, nitromethanes, acetamides). Collectively, -30 and 39% of the TOX and total organic bromine, respectively, were accounted for (on a median basis) by the sum of the measured halogenated DBPs. In addition, 28 new, previously unidentified DBPs were detected. These included brominated and iodinated haloacids, a brominated ketone, and chlorinated and iodinated aldehydes.

http://www.ncbi.nlm.nih.gov/pubmed/17180964

“3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone, better known by its historical name ‘mutagen X’ or MX, Although the precise mechanism of MX-induced DNA damage is not known, MX is able to cause DNA damagethrough an unusual mechanism of ionizing DNA bases due to its extremely high reductive potential. MX may also cause mutations through DNA adduction.”

Journal Of Environmental Science And Health Part C
Environmental Carcinogenesis And Ecotoxicology Reviews • October 2005

Carcinogenicity of the chlorination disinfection by-product MX

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Abstract

3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone, better known by its historical name ‘mutagen X’ or MX, is a chlorination disinfection by-product that forms from the reaction of chlorine and humic acids in raw water. MX has been measured in drinking water samples in several countries at levels that ranged from non-detectable to 310 ng/L. Although the concentration of MX in drinking water is typically 100- to 1000-fold lower than other common chlorinated by-products of concern (e.g., trihalomethanes), some have hypothesized that MX might play a role in the increased cancer risks that have been associated with the consumption of chlorinated water. This hypothesis is based on observations that MX, in some test systems, is extremely potent relative to trihalomethanes in inducing DNA damage and altering pathways involved in cell growth, and that in some epidemiological studies increased cancer rates are associated with the bacterial mutagenicity of disinfected water of which MX contributes a significant portion. MX also appears to be more potent than other chlorination by-products in causing cancer in animals. This article reviews the available evidence on the carcinogenicity of MX. MX induced cancer at multiple sites in male and female rats, acted as a tumor initiator and promoter, enhanced tumor yields in genetically modified rodents, induced a myriad of genotoxic effects in numerous in vitro and in vivo test systems, and was a potent inhibitor of gap junction intercellular communication. Although the precise mechanism of MX-induced DNA damage is not known, MX is able to cause DNA damage through an unusual mechanism of ionizing DNA bases due to its extremely high reductive potential. MX may also cause mutations through DNA adduction. This article develops a mean cancer potency estimate for MX of 2.3 (mg/kg-d)(-1) and an upper 95% percentile estimate of 4.5 (mg/kg-d)(-1), and examines the potential health risks posed by this chlorination contaminant in drinking water. A discussion of additional data that would be desirable to better characterize the risks posed by MX and other halogenated hydroxyfuranones follows.

http://www.ncbi.nlm.nih.gov/pubmed/16291527

Environmental Science And Technology • September 2004

Chemical and biological characterization of newly discovered iodoacid drinking water disinfection byproducts

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http://www.ncbi.nlm.nih.gov/pubmed/15487777

"Iodoacid drinking water disinfection byproducts (DBPs) were recently uncovered in drinking water samples from source water with a high bromide/iodide concentration that was disinfected with chloramines."

"The purpose of this paper is to report the analytical chemical identification of iodoacetic acid (IA) and other iodoacids in drinking water samples, to address the cytotoxicity and genotoxicity ..."

Abstract

Iodoacid drinking water disinfection byproducts (DBPs) were recently uncovered in drinking water samples from source water with a high bromide/iodide concentration that was disinfected with chloramines. The purpose of this paper is to report the analytical chemical identification of iodoacetic acid (IA) and other iodoacids in drinking water samples, to address the cytotoxicity and genotoxicity of IA in Salmonella typhimurium and mammalian cells, and to report a structure-function analysis of IA with its chlorinated and brominated monohalogenated analogues. The iodoacid DBPs were identified as iodoacetic acid, bromoiodoacetic acid, (Z)- and (E)-3-bromo-3-iodo-propenoic acid, and (E)-2-iodo-3-methylbutenedioic acid. IA represents a new class (iodoacid DBPs) of highly toxic drinking water contaminants. The cytotoxicity of IA in S. typhimurium was 2.9x and 53.5x higher than bromoacetic acid (BA) and chloroacetic acid (CA), respectively. A similar trend was found with cytotoxicity in Chinese hamster ovary (CHO) cells; IA was 3.2x and 287.5x more potent than BA and CA, respectively. This rank order was also expressed in its genotoxicity with IA being 2.6x and 523.3x more mutagenic in S. typhimurium strain TA100 than BA and CA, respectively. IA was 2.0x more genotoxic than BA and 47.2x more genotoxic than CA in CHO cells. The rank order of the toxicity of these monohalogenated acetic acids is correlated with the electrophilic reactivity of the DBPs. IA is the most toxic and genotoxic DBP in mammalian cells reported in the literature. These data suggest that chloraminated drinking waters that have high bromide and iodide source waters may contain these iodoacids and most likely other iodo-DBPs. Ultimately, it will be important to know the levels at which these iodoacids occur in drinking water in order to assess the potential for adverse environmental and human health risks.

Environmental Science & Technology • September 2003

Tribromopyrrole, brominated acids, and other disinfection byproducts produced by disinfection of drinking water rich in bromide

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Abstract

Using gas chromatography/mass spectrometry (GC/MS), we investigated the formation of disinfection by-products (DBPs) from high bromide waters (2 mg/L) treated with chlorine or chlorine dioxide used in combination with chlorine and chloramines. This study represents the first comprehensive investigation of DBPs formed by chlorine dioxide under high bromide conditions. Drinking water from full-scale treatment plants in Israel was studied, along with source water (Sea of Galilee) treated under carefully controlled laboratory conditions. Select DBPs (trihalomethanes, haloacetic acids, aldehydes, chlorite, chlorate, and bromate) were quantified. Many of the DBPs identified have not been previously reported, and several of the identifications were confirmed through the analysis of authentic standards. Elevated bromide levels in the source water caused a significant shift in speciation to bromine-containing DBPs; bromoform and dibromoacetic acid were the dominant DBPs observed, with very few chlorine-containing compounds found. Iodo-trihalomethanes were also identified, as well as a number of new brominated carboxylic acids and 2,3,5-tribromopyrrole, which represents the first time a halogenated pyrrole has been reported as a DBP. Most of the bromine-containing DBPs were formed during pre-chlorination at the initial reservoir, and were not formed by chlorine dioxide itself. An exception was the iodo-THMs, which appeared to be formed by a combination of chlorine dioxide with chloramines or chlorine (either added deliberately or as an impurity in the chlorine dioxide). A separate laboratory study was also conducted to quantitatively determine the contribution of fulvic acids and humic acids (from isolated natural organic matter in the Sea of Galilee) as precursor material to several of the DBPs identified. Results showed that fulvic acid plays a greater role in the formation of THMs, haloacetic acids, and aldehydes, but 2,3,5-tribromopyrrole was produced primarily from humic acid. Because this was the first time a halopyrrole has been identified as a DBP, 2,3,5-tribromopyrrole was tested for mammalian cell cytotoxicity and genotoxicity. In comparison to other DBPs, 2,3,5-tribromopyrrole was 8x, 4.5x, and 16x more cytotoxic than dibromoacetic acid, 3-chloro-4-(dichloromethyl)-5-hydroxy-2-[5H]-furanone [MX], and potassium bromate, respectively. 2,3,5-Tribromopyrrole also induced acute genomic damage, with a genotoxic potency (299 microM) similar to that of MX.

http://www.ncbi.nlm.nih.gov/pubmed/12967096

TAP WATER DISINFECTION BY-PRODUCTS

"Results showed that fulvic acid plays a greater role in the formation of THMs, haloacetic acids, and aldehydes, but 2,3,5-tribromopyrrole was produced primarily from humic acid. Because this was the first time a halopyrrole has been identified as a DBP, 2,3,5-tribromopyrrole was tested for mammalian cell cytotoxicity and genotoxicity. In comparison to other DBPs, 2,3,5-tribromopyrrole was 8x, 4.5x, and 16x more cytotoxic than dibromoacetic acid, 3-chloro-4-(dichloromethyl)-5-hydroxy-2-[5H]-furanone [MX], and potassium bromate, respectively. 2,3,5-Tribromopyrrole also induced acute genomic damage, with a genotoxic potency (299 microM) similar to that of MX."

“Bromoacetic Acid was over 400x more genotoxic than potassium bromate. The brominated haloacetic acids (HAAs) were more cytotoxic and genotoxic than their chlorinated analogs.”

Environmental And Molecular Mutagenesis • December 2002

Mammalian cell cytotoxicity and genotoxicity analysis of drinking water disinfection by-products

Author information

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Abstract

Cytotoxicity and genotoxicity assays were used to analyze drinking water disinfection by-products (DBPs) in Chinese hamster ovary (CHO) AS52 cells. The DBPs were chosen because they are common in drinking water, resulting from conventional disinfection using chlorination and chloramination. Data were also available to compare these results with cytotoxicity and mutagenicity studies in Salmonella typhimurium. The rank order in decreasing chronic cytotoxicity measured in a microplate-based assay was bromoacetic acid (BA) >> 3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]-furanone (MX) > dibromoacetic acid (DBA) > chloroacetic acid (CA) > KBrO(3) > tribromoacetic acid (TBA) > EMS (ethylmethanesulfonate, positive control) > dichloroacetic acid (DCA) > trichloroacetic acid (TCA). The induction of DNA strand breaks by these agents was measured by alkaline single-cell gel electrophoresis (SCGE, comet assay) and the rank order in decreasing genotoxicity was BA >> MX > CA > DBA > TBA > EMS > KBrO(3), while DCA and TCA were refractory. BA was more cytotoxic (31x) and genotoxic (14x) than MX in CHO cells. BA was over 400x more genotoxic than potassium bromate. The brominated haloacetic acids (HAAs) were more cytotoxic and genotoxic than their chlorinated analogs. The HAAs expressed a statistically significant inverse relationship in CHO cell cytotoxicity and genotoxicity as a function of increased numbers of halogen atoms per molecule. A quantitative comparison was conducted with results from a previous study with cytotoxicity and mutagenicity in S. typhimurium. There was no correlation between chronic CHO cell and bacterial cell cytotoxicity. DBP-induced CHO cell cytotoxicity was not related to mutagenic potency in S. typhimurium. Cytotoxicity in CHO cells was statistically significant and highly correlated to CHO cell genotoxicity. Finally, we determined that the DBP genotoxic potency in CHO cells and the mutagenic potency in S. typhimurium were not related. This suggests that toxicity data in S. typhimurium did not quantitatively predict the toxic effects of DBPs in mammalian cell systems. The microplate CHO cell cytotoxicity and genotoxicity assays were well suited for the analysis of DBPs, especially when the quantity of test material is limited.

http://www.ncbi.nlm.nih.gov/pubmed/12203407

CHAPTER THIRTY-TWO

Alcoholic Beverages

The Peer Review

WHAT'S IN YOUR ALCOHOLIC BEVERAGE?

Ethyl carbamate (also called urethane) is a chemical compound with the molecular formula C3H7NO2 first prepared in the nineteenth century. Structurally, it is an ester of carbamic acid. Despite its common name, it is not a component of polyurethanes. Ethyl carbamate is a white crystalline substance produced by the action of ammonia on ethyl chloroformate or by heating urea nitrate and ethyl alcohol.

Ethyl carbamate has been produced commercially in the United States for many years. It has been used as an antineoplastic agent and for other medicinal purposes but this ended after it was discovered to be carcinogenic in 1943. However, Japanese usage in medical injections continued and from 1950 to 1975 an estimated 100 million 2 ml ampules of 7 to 15% solutions of ethyl carbamate were injected into patients as a co-solvent in water for dissolving water-insoluble analgesics used for post-operation pain. These doses were estimated by Nomura (Cancer Research, 35, 2895–2899, October 1975) to be at levels that are carcinogenic in mice. This practice was stopped in 1975. "This regrettable medical situation appears to have involved the largest number (millions) of humans exposed to the largest doses of a pure carcinogen that is on record" (Japanese Journal of Cancer Research, 82, 1323–1324, December 1991). The author, U.S. cancer researcher James A. Miller, called for studies to determine the effects on Japanese cancer rates to be performed but apparently none were ever done.

Prior to World War II, ethyl carbamate saw relatively heavy use in the treatment of multiple myeloma before it was found to be toxic, carcinogenic and largely ineffective. By US FDA regulations, ethyl carbamate has been withdrawn from pharmaceutical use. However, small quantities of ethyl carbamate are also used in laboratories as an anesthetic for animals.

Ethyl carbamate was upgraded to a Group 2A carcinogen by IARC in 2007.

Formerly, crosslinking agents for permanent press textile treatments were synthesized from ethyl carbamate.

ETHYL CARBAMATE IN FOOD & BEVERAGES

The discovery of the widespread presence of ethyl carbamate in alcoholic beverages first occurred during the mid-1980s. To raise public awareness of this issue, the U.S. Center for Science in the Public Interest published, in 1987, Tainted Booze: The Consumer's Guide to Urethane in Alcoholic Beverages. Studies have shown that most, if not all, yeast-fermented alcoholic beverages contain traces of ethyl carbamate (15 ppb to 12 ppm). Other foods and beverages prepared by means of fermentation also contain ethyl carbamate. For example, bread has been found to contain 2 ppb; as much as 20 ppb has been found in some samples of soy sauce. Amounts of both ethyl carbamate and methyl carbamate have also been found in wines, sake, beer, brandy, whiskey and other fermented alcoholic beverages. It has been shown that ethyl carbamate forms from the reaction of ethanol with urea:

This reaction occurs much faster at higher temperatures, and therefore higher concentrations of ethyl carbamate are found in beverages that are heated during processing, such as brandy, whiskey, and other distilled beverages. Additionally, heating after bottling either during shipping or in preparation will cause ethyl carbamate levels to rise further.

The urea in wines results from the metabolism of arginine or citrulline by yeast or other organisms. The urea waste product is initially metabolised inside the yeast cell until it builds up to a certain level. At that point, it is excreted externally where it is able to react with the alcohol to create ethyl carbamate.

In 1988, wine and other alcoholic beverage manufacturers in the United States agreed to control the level of ethyl carbamate in wine to less than 15 ppb and in stronger alcoholic drinks to less than 125 ppb. Although the urea cannot be eliminated, it can be minimized by controlling the fertilization of grape vines, minimizing their heat exposure, using self-cloning yeast and other actions. Furthermore,

some strains of yeast have been developed to help reduce ethyl carbamate during commercial production of alcoholic beverages.

Another important mechanism for ethyl carbamate formation in alcoholic beverages is the reaction from cyanide as a precursor, which causes comparably high levels in spirits derived from cyanogenic plants (i.e. predominantly stone-fruit spirits and cachaça).

HAZARDS

Ethyl carbamate is not acutely toxic to humans, as shown by its use as a medicine. Acute toxicity studies show that the lowest fatal dose in rats, mice, and rabbits equals 1.2 grams/kg or more. When ethyl carbamate was used medicinally, about 50 percent of the patients exhibited nausea and vomiting, and long time use led to gastroenteric hemorrhages. The compound has almost no odor and a cooling, saline, bitter taste.

Studies with rats, mice, and hamsters have shown that ethyl carbamate will cause cancer when it is administered orally, injected, or applied to the skin, but no adequate studies of cancer in humans caused by ethyl carbamate have been reported due to the ethical considerations of such studies. However, in 2007, the International Agency for Research on Cancer raised ethyl carbamate to a Group 2A carcinogen that is "probably carcinogenic to humans," one level below fully carcinogenic to humans. IARC has stated that ethyl carbamate can be "reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals." In 2006, the Liquor Control Board of Ontario in Canada rejected imported cases of sherry due to excessive levels of ethyl carbamate.

Alcoholic beverages, particularly certain stone-fruit spirits and whiskies, tend to contain much higher concentrations of urethane. Heating (e.g., cooking) the beverage increases the ethyl carbamate content, and some concern exists over shipping wines to overseas markets in containers that tend to overheat. In addition, urethane has a tendency to accumulate in the human body from a number of daily dietary sources, e.g., alcohols, bread and other fermented grain products, soy sauce, orange juice and commonly consumed foods. Hence, exposure risk to human health is increasingly evaluated on the total ethyl carbamate intake from the daily diet (WHO refers to this as "margin of exposure" or MOE), of which alcoholic beverages often provide the most significant portion.
Studies in Korea (2000) and Hong Kong (2009) outline the extent of the accumulative exposure to ethyl carbamate in daily life. Fermented foods such as soy sauce, kimchi, soybean paste, breads, rolls, buns, crackers and bean curd, along with wine, sake and plum wine, were found to be the foods with the highest ethyl carbamate levels in traditional Asian diets. In 2005, the JECFA (Joint FAO/WHO Expert Committee On Food Additives) risk assessment evaluation of ethyl carbamate concluded that the MOE intake of ethyl carbamate from daily food and alcoholic beverages combined is of concern and mitigation measures to reduce ethyl carbamate in some alcoholic beverages should continue. There is little doubt that ethyl carbamate in alcoholic beverages is very important to health authorities, while the cumulative daily exposure in the typical diet is also an issue of rising concern that merits closer observation. The Korean study concluded, "It would be desirable to closely monitor ethyl carbamate levels in Korean foods and find ways to reduce the daily intake."

DETECTION IN ALCOHOLIC BEVERAGES

The concerns raised by the toxicological aspects of EC together with the low concentration levels (µg/L) found in wines, as well as the occurrence of interferences on detection, has motivated several researchers to develop new methods to determine it in wines. Several extraction and chromatographic techniques have been used, including continuous liquid–liquid extraction (LLE) with Soxhlet apparatus, derivatization with 9-xanthydrol followed by high-pressure liquid chromatography (HPLC) with fluorescence detection and even LLE after derivatization, followed by gas chromatography coupled with mass spectrometry detection (GC–MS).

On the other hand, the reference method set by the International Organization of Vine and Wine (OIV) uses solid phase extraction (SPE) preceding GC–MS quantification. Other methods also make use of SPE, but use gas chromatography with mass spectrometry (MDGC/MS) and liquid chromatography with tandem mass spectrometry (LC–MS/MS) for detection. Most of the methodologies found in the literature to quantify EC use gas chromatography, using LLE and SPE as extraction techniques. Nevertheless, several efforts have also been done to develop new methodologies to determine EC without using long procedures and hard-working analyses, combining precision to high sensitivity.

In this regard, headspace solid phase microextraction (HS-SPME) has been gaining great highlighting and alternative methodologies have been proposed using the most recent identification and quantification technology, such as gas chromatography with tandem mass spectrometry detection (GC–MS/MS) and two-dimensional gas chromatography with time-of-flight mass spectrometry (GC × GC–ToFMS).

Microextraction by packed sorbent (MEPS) has also becoming emergent, arising as a feasible and easy-to-use extraction technique. Recently a simple and sensitive methodology was developed and optimized to quantify EC in wines using MEPS extraction, through a hand-held automated analytical syringe, with GC–MS detection. MEPS/GC–MS methodology is an excellent tool to quantify EC in wines, gathering efficiency and effectiveness, without using long and hard-working procedures.

RELATED COMPOUNDS

Other carbamates include methyl carbamate (urethylane, m. p. 52-54 °C), butyl carbamate, and phenyl carbamate (m. p. 149-152 °C), which can also be prepared from the corresponding chloroformate and ammonia. These esters are white, crystalline solids at room temperature. Except for the phenyl carbamate, they sublime at moderate temperatures; methyl carbamate sublimes at room temperatures. The first two and ethyl carbamate are very soluble in water, benzene, and ether. These other carbamates (methyl, butyl, and phenyl) are only used in small quantities for research purposes.

F1000 Research • May 2016

Substance use during pregnancy

Author information

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Abstract

“Prenatal substance use is a critical public health concern that is linked with several harmful maternal and fetal consequences. The most frequently used substance in pregnancy is tobacco, followed by alcohol, cannabis and other illicit substances. Unfortunately, polysubstance use in pregnancy is common, as well as psychiatric comorbidity, environmental stressors, and limited and disrupted parental care, all of which can compound deleterious maternal and fetal outcomes. There are few existing treatments for prenatal substance use and these mainly comprise behavioral and psychosocial interventions. Contingency management has been shown to be the most efficacious of these. The purpose of this review is to examine the recent literature on the prenatal use of tobacco, alcohol, cannabis, stimulants, and opioids, including the effects of these on maternal and fetal health and the current therapeutic options.”

Full text with 127 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4870985/

THE SKINNY ON SPIRITS

WHERE'S THAT NUTRITION INFO?

Where's the Alcohol Nutrition Info?

Manufacturers are not required to list full nutritional information for beer. So by popular demand, we put together some information on beer nutrition. It's based on a 12 oz can of regular beer (about 1/3 of a liter).

The good news is that beer is fat free, cholesterol free and has no regular sugars. The sugar used in processing turns into alcohol - that's where most of the calories come from. Beers with higher percentages of alcohol have more calories - so bock, triple bock, etc. will pack more calories per serving than a regular beer.

One regular beer is about 150 calories, 13 grams of carbs and about 14 grams of alcohol. A typical light beer has about 110 calories, 7 grams of carbs and 12 grams of alcohol. A very light beer has around 95 calories, 3 grams of carbs and 12 grams of alcohol.

Enjoy your beer and remember that 3 cans of beer = 450 calories, which is almost a quarter of your daily calories (2000 calorie a day diet).

Calories

Each gram of alcohol has 7 calories. Compare that to 4 calories per gram of carb, or 9 calories per gram of fat. That means a spirt has about 97 calories per shot, a glass of wine has about 123 calories per glass and a beer has about 154 calories per glass!. Alcoholic beverage producers are not mandated to label their products with nutrition information. We bring you estimated nutrition information based on the following standard serving sizes:

- beer - 12 fluid ounces
- wine - 5 fluid ounces
- spirits - 1.5 fluid ounces

Light Beer vs. Regular Beer

Light beer is light because it has less calories. But how do they do it? Alcohol in general is high in calories, so the only way to dramatically cut the calories is to cut the alcohol. Budweiser Select, for example, has only 2.4% alcohol (variable). Other light beers also have less alcohol than their "regular" versions. And do they have less flavor? Depends on who you ask. If you're a beer aficionado or are going to savor a beer with dinner, we say choose taste over calories. While one beer can add up to anywhere from 100-200 calories, two light beers will be about the same. Please drink responsibly and never, ever drive after the first pleasing taste of your favorite alcoholic beverage. Driving under the influence, according to the peer review, and no shortage of it, leads to brutal head injuries, loss of limbs, neurological disorders including paraplegic and quadraplegic conditions and most often, dismemberment and death. Life in jail is also a frequent and expected prognosis.

“Here, we review recent insights into the rewarding effects of alcohol, as they pertain to different nAChR subtypes, associated signaling molecules, and pathways that contribute to the molecular mechanisms of alcoholism and/or comorbid brain disorders.”

Progress In Molecular Biology And Translational Science • January 2016

Recent Advances in Nicotinic Receptor Signaling in Alcohol Abuse and Alcoholism

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Abstract

Alcohol is the most commonly abused legal substance and alcoholism is a serious public health problem. It is a leading cause of preventable death in the world. The cellular and molecular mechanisms of alcohol reward and addiction are still not well understood. Emerging evidence indicates that unlike other drugs of abuse, such as nicotine, cocaine, or opioids, alcohol targets numerous channel proteins, receptor molecules, and signaling pathways in the brain. Previously, research has identified brain nicotinic acetylcholine receptors (nAChRs), a heterogeneous family of pentameric ligand-gated cation channels expressed in the mammalian brain, as critical molecular targets for alcohol abuse and dependence. Genetic variations encoding nAChR subunits have been shown to increase the vulnerability to develop alcohol dependence. Here, we review recent insights into the rewarding effects of alcohol, as they pertain to different nAChR subtypes, associated signaling molecules, and pathways that contribute to the molecular mechanisms of alcoholism and/or comorbid brain disorders. Understanding these cellular changes and molecular underpinnings may be useful for the advancement of brain nicotinic-cholinergic mechanisms, and will lead to a better translational and therapeutic outcome for alcoholism and/or comorbid conditions.

http://www.ncbi.nlm.nih.gov/pubmed/26810002

“Fetal alcohol spectrum disorders (FASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are associated with a range of neurocognitive impairments. Executive functioning deficits are a hallmark feature of both disorders.”

Journal Of Attention Disorders • January 2016

Comparing Executive Functioning in Children and Adolescents With Fetal Alcohol Spectrum Disorders and ADHD: A Meta-Analysis

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Abstract

OBJECTIVE

Fetal alcohol spectrum disorders (FASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are associated with a range of neurocognitive impairments. Executive functioning deficits are a hallmark feature of both disorders.

METHOD

The present meta-analysis was undertaken to disentangle the behavioral phenotype of FASD and ADHD by quantitatively differentiating executive functioning differences between these two groups. The current meta-analysis reviews 15 studies comparing children and adolescents with FASD and ADHD to typically developing (TD) samples, on a variety of executive function measures.

RESULTS

Results indicate that when compared with TD samples, FASD and ADHD samples demonstrate significant executive function deficits ($d = 0.82$ and $d = 0.55$, respectively). In addition, FASD samples experience significantly greater deficits when compared with ADHD samples ($d = 0.25$). Results were moderated by IQ and socioeconomic status.

CONCLUSION

These findings further our understanding of the cognitive differences between FASD and ADHD samples and have the potential to influence future basic research, assessment, and intervention.

http://www.ncbi.nlm.nih.gov/pubmed/26729621

“Malnutrition is common in hospitalized patients with cirrhosis, and patients with malnutrition showed a trend toward increased complications and mortality. Severe malnutrition, as identified by subjective global assessment, and advanced cirrhosis were predictors of in-hospital mortality.”

Journal Of The Medical Association Of Thailand • February 2016

Nutritional Status and its Impact on Clinical Outcomes for Patients Admitted to Hospital with Cirrhosis

Author information
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Abstract

BACKGROUND

In patients with cirrhosis, nutritional status is an important predictor of clinical outcomes that can be assessed in clinical practice using conventional methods. Previous studies have shown that malnutrition is associated with increased morbidity and mortality in patients with cirrhosis. However, there have been very few reports from Southeast Asia.

OBJECTIVE

To determine the prevalence of malnutrition in patients with cirrhosis who are admitted to hospital and to assess its correlation with mortality, complications, length of stay, and total cost of hospitalization.

MATERIAL AND METHOD

This prospective non-interventional study included 60 consecutive patients with cirrhosis admitted to Rajavithi Hospital, Bangkok, Thailand, from August 2013 to February 2014. Baseline demographic and clinical data during their hospitalizations were collected prospectively. Nutritional status was assessed by subjective global assessment (SGA) and anthropometry (body mass index (BMI) and mid-arm circumference (MAC)). Malnutrition was defined as SGA class B/ C and MAC of < 5th percentile of the age- and gender-matched reference population.

RESULTS

Of the 60 patients, 70% were male. The most common causes of cirrhosis were alcohol (50%) and hepatitis C infection (35%). Most patients were classified as Child-Pugh class B (41.7%) or C (36.7%). The mortality rate was 26.7%, and the most common complications were infections (60%) and renal failure (43.3%). The median length of stay in hospital was 8.5 (1-51) days, with a median cost of 1,163 (183-9,969) US dollars. The prevalence of malnutrition varied between 18% and 92% depending on the assessment method employed: 18% were considered malnourished when assessed by BMI, 63% by MAC, 78% by serum albumin, 65% by absolute lymphocyte count, and 92% by SGA. Patients with malnutrition showed a trend toward increased mortality, complications, length of hospital stay and cost; however, the differences were not statistically significant. Significant predictors of mortality included Child-Pugh class B (16% mortality) and C (50% mortality), severe malnutrition as assessed by SGA (35% mortality), presence of ascites (relative risk, RR: 2.3), hepatic encephalopathy (RR: 2.5), hepatorenal syndrome (RR: 4.1) and renal failure (RR: 3.3).

CONCLUSION

Malnutrition is common in hospitalized patients with cirrhosis, and patients with malnutrition showed a trend toward increased complications and mortality. Severe malnutrition, as identified by SGA, and advanced cirrhosis were predictors of in-hospital mortality.

http://www.ncbi.nlm.nih.gov/pubmed/27266216

“Attention-deficit/hyperactivity disorder (ADHD)-like symptoms are common in fetal alcohol spectrum disorders, fetal alcohol spectrum disorders, fetal alcohol syndrome disorder and ADHD groups both display executive function impairments.”

Journal Of Child Psychology And Psychiatry • February 2016

Research Review:
Executive function deficits in fetal alcohol spectrum disorders and attention-deficit/hyperactivity disorder - a meta-analysis

Author information
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Abstract

BACKGROUND
Attention-deficit/hyperactivity disorder (ADHD)-like symptoms are common in fetal alcohol spectrum disorders (FASD). FASD and ADHD groups both display executive function impairments; however, there is ongoing debate whether the pattern and magnitude of executive function deficits differs between these two types of disorders.

METHODS
An electronic literature search was conducted (PubMed, PsychInfo; 1972-2013) to identify studies comparing the executive functioning of children with FASD with ADHD or control groups. FASD groups included those with and without dysmorphy (i.e., FAS, pFAS, ARND, and other FASD diagnoses). Effect sizes (Hedges' g, standardized mean difference) were calculated. Random effects meta-analytic models were performed using the metafor package for R.

RESULTS
Fifty-one studies met inclusion criteria (FASD N = 2,115; ADHD N = 453; controls N = 1,990). Children with FASD showed the strongest and most consistent deficits in planning, fluency, and set-shifting compared to controls (Hedges' g = -0.94, -0.78) and children with ADHD (Hedges' g = -0.72, -0.32). FASD was associated with moderate to large impairments in working memory, compared to controls (Hedges' g = -.84, -.58) and small impairments relative to groups with ADHD (Hedges' g = -.26). Smaller and less consistent deficits were found on measures of inhibition and vigilance relative to controls (Hedges' g = -0.52, -0.31); FASD and ADHD were not differentiated on these measures. Moderator analyses indicated executive dysfunction was associated with older age, dysmorphy, and larger group differences in IQ. Sex and diagnostic system were not consistently related to effect size.

CONCLUSIONS
While FASD is associated with global executive impairments, executive function weaknesses are most consistent for measures of planning, fluency, and set-shifting. Neuropsychological measures assessing these executive function domains may improve differential diagnosis and treatment of FASD.

http://www.ncbi.nlm.nih.gov/pubmed/26251262

“These findings support that alcohol has deleterious effects on global and regional Gray Matter above and beyond age ...”

Human Brain Mapping • March 2016

Negative and interactive effects of sex, aging, and alcohol abuse on gray matter morphometry

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Abstract

Chronic alcohol use is associated with declines in gray matter (GM) volume, as is the normal aging process. Less apparent, however, is how the interaction between aging and heavy alcohol use affects changes in GM across the lifespan. There is some evidence that women are more vulnerable to the negative effects of alcohol use on GM than men. In the current study, we examined whether localized GM was related to measures of alcohol use disorder (e.g., AUDIT score) in a large sample (N=436) of participants, ages 18-55 years, with a range of disease severity, using both voxel-based morphometry (VBM) and surface-based morphometry (SBM). We also explored whether GM associations with alcohol use disorder (AUD) severity are moderated by sex and age. Results showed significant negative associations between AUD severity and GM volume throughout temporal, parietal, frontal, and occipital lobes. Women showed more negative effects of alcohol use than men for cortical thickness in left orbitofrontal cortex, but evidence for increased vulnerability based on sex was limited overall. Similarly, a specific age by alcohol use interaction was observed for volume of right insula, but other regional or global interactions were not statistically supported. However, significant negative associations between heavy alcohol use and GM volumes were observed as early as 18-25 years. These findings support that alcohol has deleterious effects on global and regional GM above and beyond age, and, of particular importance, that regional associations emerge in early adulthood.

http://www.ncbi.nlm.nih.gov/pubmed/26947584

“Findings suggest that reduced cortical connectivity in Heavy drinkers contribute to decline in cognitive abilities associated with heavy alcohol consumption, whereas increased cerebellar connectivity in Heavy drinkers may have compensatory effects on behavioral performance. The results reveal how drinking history alters the association between brain functional connectivity density and individual differences in behavioral performance.”

Molecular Psychiatry • March 2016

Alcohol affects brain functional connectivity and its coupling with behavior: greater effects in male heavy drinkers

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Abstract

Acute and chronic alcohol exposure significantly affect behavior but the underlying neurobiological mechanisms are still poorly understood. Here, we used functional connectivity density (FCD) mapping to study alcohol-related changes in resting brain activity and their association with behavior. Heavy drinkers (HD, N=16, 16 males) and normal controls (NM, N=24, 14 males) were tested after placebo and after acute alcohol administration. Group comparisons showed that NM had higher FCD in visual and prefrontal cortices, default mode network regions and thalamus, while HD had higher FCD in cerebellum. Acute alcohol significantly increased FCD within the thalamus, impaired cognitive and motor functions, and affected self-reports of mood/drug effects in both groups. Partial least squares regression showed that alcohol-induced changes in mood/drug effects were associated with changes in thalamic FCD in both groups. Disruptions in motor function were associated with increases in cerebellar FCD in NM and thalamus FCD in HD. Alcohol-induced declines in cognitive performance were associated with connectivity increases in visual cortex and thalamus in NM, but in HD, increases in precuneus FCD were associated with improved cognitive performance. Acute alcohol reduced ‘neurocognitive coupling’, the association between behavioral performance and FCD (indexing brain activity), an effect that was accentuated in HD compared with NM. Findings suggest that reduced cortical connectivity in HD contribute to decline in cognitive abilities associated with heavy alcohol consumption, whereas increased cerebellar connectivity in HD may have compensatory effects on behavioral performance. The results reveal how drinking history alters the association between brain FCD and individual differences in behavioral performance.

http://www.nature.com/mp/journal/vaop/ncurrent/full/mp201625a.html

“Physicians should be aware of the association between alcohol dependence syndrome and gout occurrence ...”

Joint, Bone, Spine • May 2016

Alcohol-related diseases and alcohol dependence syndrome is associated with increased gout risk: A nationwide population-based cohort study

Author information

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Abstract

OBJECTIVE

Alcohol intake is strongly associated with hyperuricemia, which may cause gout. This study evaluated the risk of gout in patients with alcohol-related diseases and alcohol dependence syndrome.

METHODS

We used the Taiwan National Health Insurance Research Database (NHIRD) to conduct a nationwide population-based cohort study to assess the risk of gout and gout incidence in patients with alcohol-related diseases and alcohol dependence syndrome (as defined by the International Classification of Diseases, Ninth Revision). In the NHIRD records from 1998 to 2008, we identified 11,675 cases of alcohol-related diseases. The control group comprised 23,350 cases without alcohol-related diseases propensity score-matched (1 case: 2 controls) for age, age group, and sex.

RESULTS

The results revealed that alcohol-related diseases were significantly associated with gout risk (adjusted hazard ratio 1.88; $P<0.0001$). Of the alcohol-related disease cases, 34.1% of the patients had alcohol dependence syndrome (males 34.8%; females 32.4%), and alcohol dependence was independently associated with gout occurrence (relative risk [RR] 2.01; $P<0.0001$). Severe alcohol-dependent patients (who were also the heavy benzodiazepines users), were associated with an increased risk of gout (RR 1.71 to 4.21, $P\leq0.0182$).

CONCLUSION

Physicians should be aware of the association between alcohol dependence syndrome and gout occurrence, and alcohol use assessment and measures to prevent alcohol dependence should be implemented in the integrative care for patients with gout.

http://www.ncbi.nlm.nih.gov/pubmed/27238189

“Fetal alcohol syndrome (FAS) is a well-known consequence of prenatal alcohol exposure. However, women tend to deny or underreport their alcohol use during pregnancy.”

Alcoholism, Clinical And Experimental Research • May 2016

Fetal Alcohol Syndrome and Maternal Alcohol Biomarkers in Sera: A Register-Based Case-Control Study

Author information

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9. Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts

Abstract

BACKGROUND

Fetal alcohol syndrome (FAS) is a well-known consequence of prenatal alcohol exposure. However, women tend to deny or underreport their alcohol use during pregnancy. The aim of this study was to explore the usability of various alcohol biomarkers for FAS screening in a data set without information on self-reported alcohol use.

METHODS

A nationwide register study with a case-control design was conducted. The target population consisted of all live births in Finland from 1987 to 2005. FAS cases (n = 565) were identified from the Finnish Register of Congenital Malformations. Mothers of FAS cases and their controls were selected in a ratio of 1 to 2 from the Finnish Maternity Cohort (FMC). Background information was obtained from the Finnish Medical Birth Register. Serum samples, collected at the mother’s first visit to the maternity care, were obtained from the national FMC biobank. Biomarkers of alcohol consumption, gamma-glutamyltransferase (GGT), carbohydrate-deficient transferrin (%CDT), combination of GGT and CDT (GGT-CDT), and ethylglucuronide (EtG) were analyzed from mothers of FAS cases (n = 385) and their controls (n = 745).

RESULTS

Median levels of all biomarkers were significantly higher among the mothers of FAS children than in control mothers. Using previously validated cutoffs for EtG, GGT, %CDT, and GGT-CDT, nearly half (46%) of the mothers with affected offspring could be identified. The predictive association was highest for GGT-CDT combination and significant also for all the other biomarkers.

CONCLUSIONS

In this explorative case-control study, we demonstrate that the FMC biobank can be used to screen alcohol biomarkers for epidemiological research purposes. According to our results, the use of alcohol biomarkers during the first trimester may help to identify the high-risk pregnancies for FAS. A more systematic use of alcohol biomarkers at maternity care may open new possibilities for screening and intervention of alcohol use among pregnant mothers.

http://www.ncbi.nlm.nih.gov/pubmed/27228551

“Fetal alcohol spectrum disorders comprise the spectrum of cognitive, behavioral, and neurological impairments caused by prenatal alcohol exposure (PAE).”

Human Brain Mapping • May 2016

White matter deficits mediate effects of prenatal alcohol exposure on cognitive development in childhood

Author information

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Abstract

Fetal alcohol spectrum disorders comprise the spectrum of cognitive, behavioral, and neurological impairments caused by prenatal alcohol exposure (PAE). Diffusion tensor imaging (DTI) was performed on 54 children (age 10.1 ± 1.0 years) from the Cape Town Longitudinal Cohort, for whom detailed drinking histories obtained during pregnancy are available: 26 with full fetal alcohol syndrome (FAS) or partial FAS (PFAS), 15 nonsyndromal heavily exposed (HE), and 13 controls. Using voxelwise analyses, children with FAS/PFAS showed significantly lower fractional anisotropy (FA) in four white matter (WM) regions and higher mean diffusivity (MD) in seven; three regions of FA and MD differences (left inferior longitudinal fasciculus (ILF), splenium, and isthmus) overlapped, and the fourth FA cluster was located in the same WM bundle (right ILF) as an MD cluster. HE children showed lower FA and higher MD in a subset of these regions. Significant correlations were observed between three continuous alcohol measures and DTI values at cluster peaks, indicating that WM damage in several regions is dose dependent. Lower FA in the regions of interest was attributable primarily to increased radial diffusivity rather than decreased axonal diffusivity, suggesting poorer axon packing density and/or myelination. Multiple regression models indicated that this cortical WM impairment partially mediated adverse effects of PAE on information processing speed and eyeblink conditioning.

http://www.ncbi.nlm.nih.gov/pubmed/27219850

Progress In Neuropsychopharmacology, Biology And Psychiatry • May 2016

The metabolic syndrome in patients with alcohol dependency: Current research and clinical implications

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Abstract

“The relationship between alcohol dependency and disorders such as liver disease and cancer has been thoroughly researched. However, the effects of alcohol on cardiometabolic health remain controversial. Several reports found low to moderate alcohol consumption to be associated with a lower risk for cardiometabolic disorders. In contrast, excessive alcohol consumption has been related to an increased risk. Most of these studies were performed in non-clinical populations, therefore limiting the explanatory power to non-dependent patients. Only a few studies examined cardiovascular disorders and cardiovascular risk factors, in particular the metabolic syndrome (MetS), in alcohol dependent patients. We here present a narrative review of studies performed so far on the MetS in alcohol dependency, and provide current hypotheses on the association of alcohol dependency, appetite regulation and the development of the MetS.”

http://www.ncbi.nlm.nih.gov/pubmed/27174541

Alcohol And Alcoholism • June 2016

The Prevalence of Metabolic Syndrome in Alcohol Use Disorders: A Systematic Review and Meta-analysis

Author information

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Abstract

"The metabolic syndrome (MetS) and its components are highly predictive of cardiovascular diseases. Our meta-analysis demonstrates that more than 1 in 5 persons with alcohol use disorder (AUDs) has the MetS. Routine screening and multidisciplinary management of metabolic abnormalities should be an integral part of the multidisciplinary treatment of AUDs."

http://www.ncbi.nlm.nih.gov/pubmed/27337988

“These results provide a mechanism by which vodka may contribute to alcoholic liver disease and supports the notion that wine, containing resveratrol, may prevent cellular apoptosis in liver tissue in the setting of hypercholesterolemia.”

Journal Of Surgical Research • June 2016

Alcohol modulates autophagy and apoptosis in pig liver tissue

Author information
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Abstract

BACKGROUND

Autophagy serves as a cellular protective mechanism against alcohol-induced tissue injury but excessive autophagy can also be detrimental leading to apoptosis. Our laboratory has previously shown that moderate alcohol consumption alters expression of proteins in the insulin signaling pathway and worsens glucose metabolism in the liver in a swine model of metabolic syndrome. We examined the effect of alcohol consumption on apoptosis and autophagy signaling in the liver in our clinically relevant animal model of chronic hypercholesterolemia.

MATERIAL AND METHODS

Twenty-six Yorkshire swine were fed a high-fat diet for 4 wks and were then split into three groups: hypercholesterolemic diet alone (HCC, n = 9), hypercholesterolemic diet with vodka (hypercholesterolemic vodka [HCV], n = 9), and hypercholesterolemic diet with wine (hypercholesterolemic wine [HCW], n = 8) for 7 wks. Animals underwent euthanasia, and liver tissue samples were harvested for analysis. Liver tissue was analyzed via Western blot analysis. Protein density data were normalized to GAPDH and is reported as fold-change values ± standard error of the mean compared to the high-cholesterol diet control group. A Kruskal-Wallis test with a Dunn’s multiple comparison test was used to compare the means among groups.

RESULTS

The HCV group showed significant increases in several proapoptotic proteins (including caspase 3, caspase 8, caspase 9, and cleaved caspase 9) compared with the HCC group. There was a decrease in the proapoptotic protein (BAD) and an increase in anti-apoptotic signal (B-cell lymphoma-2) in the HCW group compared with HCC control. There were increases in pro-survival proteins (AKT, p-AKT, mTOR, p-mTOR) in the HCW and the HCV group compared with control (HCC). There were decreases in autophagy protein LCB-3 in the HCW and HCV compared with the control.

CONCLUSIONS

We found that moderate alcohol consumption altered protein expression related to apoptosis and autophagy signaling in pig liver in the setting of hypercholesterolemia. Interestingly, vodka may induce proapoptotic pathways in liver tissue, whereas wine may induce anti-apoptotic signaling. These results provide a mechanism by which vodka may contribute to alcoholic liver disease and supports the notion that wine, containing resveratrol, may prevent cellular apoptosis in liver tissue in the setting of hypercholesterolemia.

http://www.ncbi.nlm.nih.gov/pubmed/27338546

“Evidence shows that the brain was the most severely impacted organ of the body systems discussed. However, prenatal alcohol exposure causes several abnormalities within the heart, kidney, liver, gastrointestinal tract, and the endocrine systems.”

Birth Defects Research Part C Embryo Today • June 2016

Impact of fetal alcohol exposure on body systems: A systematic review

Author information

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Natural Sciences Division, Biology Department, Franklin Pierce University, 40 University Dr., Rindge, NH, 03461

Abstract

OBJECTIVE

Review of published manuscripts on fetal alcohol exposure on several body systems.

METHOD

Articles in this review were found online using databases such as Medline, Medline Complete, PubMed, and Health Source: Nursing/Academic Edition. The following terms were searched: fetal alcohol spectrum disorders, fetal alcohol syndrome, prenatal alcohol exposure, and alcohol related birth defects.

RESULTS

Thirteen articles were gathered, five original investigations and eight reviews. This review identified several abnormalities in the body systems discussed and their associations to fetal alcohol syndrome.

CONCLUSIONS

Evidence shows that the brain was the most severely impacted organ of the body systems discussed. However, prenatal alcohol exposure causes several abnormalities within the heart, kidney, liver, gastrointestinal tract, and the endocrine systems. In addition, preventative measures need to be taken by mothers during pregnancy.

http://www.ncbi.nlm.nih.gov/pubmed/27297122

European Journal Of Health Economics • June 2016

Societal costs of fetal alcohol syndrome in Sweden

Author information

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3. Department of Medicine and Optometry, eHealth Institute, Linnaeus University, 391 82, Kalmar, Sweden

Abstract

OBJECTIVE

To estimate the annual societal cost of fetal alcohol syndrome (FAS) in Sweden, focusing on the secondary disabilities thought feasible to limit via early interventions.

METHODS

Prevalence-based cost-of-illness analysis of FAS in Sweden for 2014. Direct costs (societal support, special education, psychiatric disorders and alcohol/drug abuse) and indirect costs (reduced working capacity and informal caring), were included. The calculations were based on published Swedish studies, including a register-based follow-up study of adults with FAS, reports and databases, and experts.

RESULTS

The annual total societal cost of FAS was estimated at €76,000 per child (0-17 years) and €110,000 per adult (18-74 years), corresponding to €1.6 billion per year in the Swedish population using a prevalence of FAS of 0.2 %. The annual additional cost of FAS (difference between the FAS group and a comparison group) was estimated at €1.4 billion using a prevalence of 0.2 %. The major cost driver was the cost of societal support.

CONCLUSIONS

The cost burden of FAS on the society is extensive, but likely to be underestimated. A reduction in the societal costs of FAS, both preventive and targeted interventions to children with FAS, should be prioritized. That is, the cost of early interventions such as placement in family homes or other forms of housing, and special education, represent unavoidable costs. However, these types of interventions are highly relevant to improve the individual's quality of life and future prospects, and also, within a long-term perspective, to limit the societal costs and personal suffering.

http://www.ncbi.nlm.nih.gov/pubmed/27279344

“In conclusion, moderate Red Wine consumption is associated with a lower prevalence of the Metabolic Syndrome in an elderly Mediterranean population at a high cardiovascular risk.”

British Journal Of Nutrition • April 2015

Moderate red wine consumption is associated with a lower prevalence of the metabolic syndrome in the PREDIMED population

Author information

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Abstract

Previous studies on the association between alcohol intake and the development of the metabolic syndrome (MetS) have yielded inconsistent results. Besides, few studies have analysed the effects of red wine (RW) consumption on the prevalence of the MetS and its components. As moderate RW drinkers have a better lipid profile and lower incidence rates of diabetes, hypertension and abdominal obesity, all components of the MetS, it was hypothesised that moderate RW consumption could be associated with a lower prevalence of the MetS. In the present cross-sectional study of 5801 elderly participants at a high cardiovascular risk included in the PREDIMED (Prevención con Dieta Mediterránea) study, 3897 fulfilled the criteria of the MetS at baseline. RW intake was recorded using a validated 137-item FFQ. Multiple logistic regression analysis was carried out to estimate the association between RW intake and the prevalence of the MetS. Compared with non-drinkers, moderate RW drinkers (≥ 1 drink/d) were found to have a reduced risk of prevalent MetS (OR 0.56, 95 % CI 0.45, 0.68; $P < 0.001$), a lower risk of having an abnormal waist circumference (OR 0.59, 95 % CI 0.46, 0.77; $P < 0.001$), low HDL-cholesterol concentrations (OR 0.42, 95 % CI 0.32, 0.53; $P < 0.001$), high blood pressure (OR 0.28, 95 % CI 0.17, 0.45; $P < 0.001$) and high fasting plasma glucose concentrations (OR 0.67, 95 % CI 0.54, 0.82; $P < 0.001$) after adjusting for several confounders. This association was found to be stronger in female participants, in participants aged < 70 years and in participants who were former or current smokers. No significant association was found between RW intake (≥ 1 drink/d) and TAG concentrations. In conclusion, moderate RW consumption is associated with a lower prevalence of the MetS in an elderly Mediterranean population at a high cardiovascular risk.

http://www.ncbi.nlm.nih.gov/pubmed/26148915

Child Neuropsychology • July 2015

Executive functioning deficits in preschool children with Fetal Alcohol Spectrum Disorders

Author information

Fuglestad AJ1, Whitley ML1, Carlson SM2, Boys CJ1, Eckerle JK3, Fink BA1, Wozniak JR1.

Abstract

“Executive function (EF) deficit is a hallmark of Fetal Alcohol Spectrum Disorders (FASD), but the vast majority of available evidence comes from school-age children and adolescents. Very little is known about EF during the critical developmental period prior to 6 years of age in FASD. We evaluated EF in 39 children with FASD (3.0-5.5 years) and a comparison group of 50 age-matched, nonexposed controls. Measures included the EF Scale for Early Childhood and a Delay of Gratification task. Compared to age-matched controls, preschool children with FASD had impairments on the EF Scale and showed more impulsivity on the Delay of Gratification task. To confirm the EF Scale finding, FASD group performance was compared to a separate normative dataset (N = 1,400). Those with FASD performed below normal (M = -0.57, SD = 0.92). Within the FASD group, IQ was correlated with the EF Scale (partial r = .60, p = .001) and Delay of Gratification (partial r = .58, p = .005). EF Scale performance did not differ significantly across levels of FASD severity (fetal alcohol syndrome [FAS], partial FAS, or alcohol-related neurobehavioral disorder [ARND]). However, compared to normative data, those with FAS had the largest deficits (M = -0.91 SD from the mean, SE = 0.23), followed by partial FAS (M = -0.66 SD from the mean, SE = 0.26), then ARND (M = -0.36 SD from the mean, SE = 0.20). These novel data show that EF deficits manifest well before the age of 6 years in children with FASD, that they occur across the spectrum, and that EF may be most impaired in children with more severe forms of FASD and/or lower IQs.”

http://www.ncbi.nlm.nih.gov/pubmed/25011516

Indian Psychiatry Journal • July 2015

Central pontine myelinolysis in a case of alcohol dependence syndrome

Author information

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3. Department of Psychiatry, Base Hospital, New Delhi, India
4. Department of Psychiatry, INHS Asvini, Mumbai, Maharashtra, India

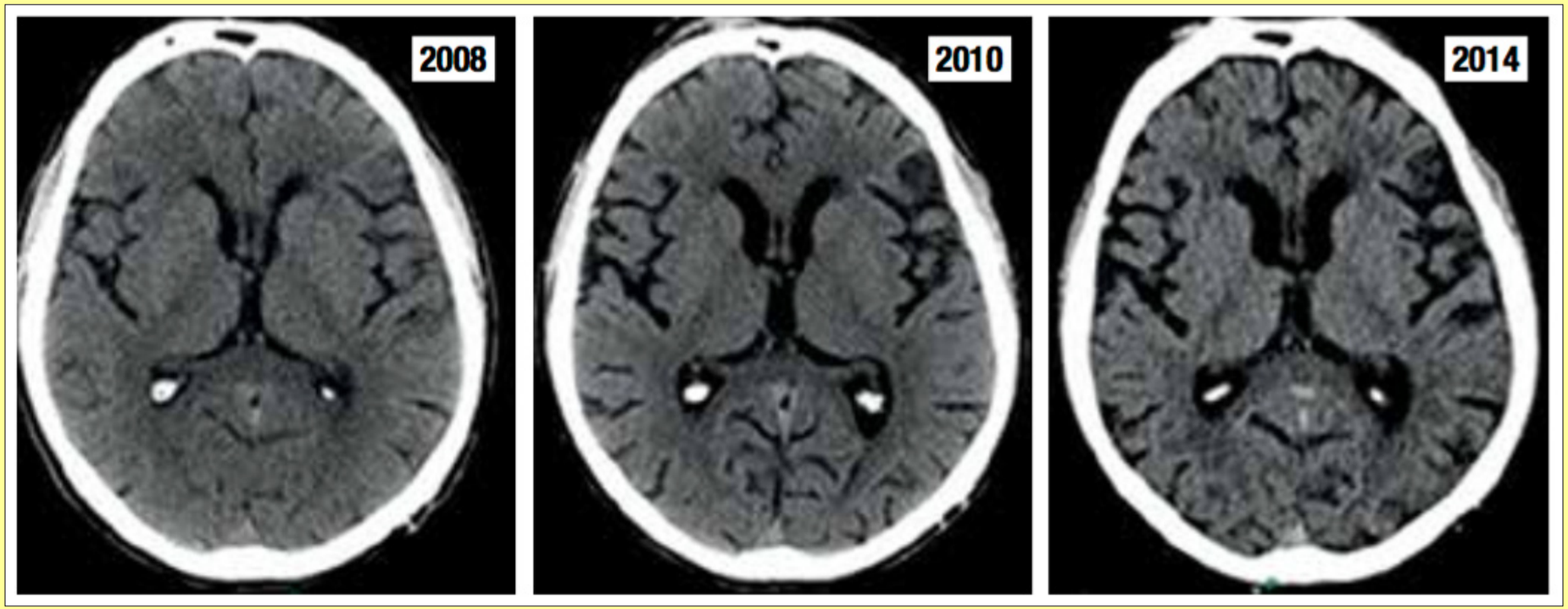
Abstract

“Osmotic Demyelination Syndrome includes Central Pontine Myelinolysis and Extrapontine Myelinolysis. This condition has been described in cases of chronic Alcohol Dependence Syndrome and in rapid correction of hyponatremia. Though we frequently see patients with Alcohol Dependence Syndrome presenting with complicated withdrawal, Central Pontine Myelinolysis remains largely undetected and under-reported in literature. We present here a case of protracted Delirium Tremens where MRI brain revealed Central Pontine Myelinolysis. Subsequently cognitive assessment revealed significant dysfunction and brain SPECT showed hypo-perfusion of the frontal lobes. Osmotic Demyelination Syndrome should be suspected in protracted Delirium Tremens.”

Full text, photos, graphs, charts and 9 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4866352/

CT scan of the brain, below, repeated over a 6 year period, showing progressive central and peripheral brain atrophy. The brain's gray matter is shrinking and the reduction, clearly seen from left to right, causes dysfunction in executive decision making and thought processing.



Progressive Deterioration Of Gray Matter Brain CT Scan Images (above) Courtesy Of:

Progressive Brain atrophy due to chronic alcohol abuse

By Gleb Slobodin MD and Majed Odeh MD • October 2015
Department of Internal Medicine A, Bnai Zion Medical Center
affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

https://www.ima.org.il/FilesUpload/IMAJ/0/172/86478.pdf

Progressive Brain atrophy due to chronic alcohol abuse

By Gleb Slobodin MD and Majed Odeh MD • October 2015
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A 43 year-old man was brought to the emergency room with head trauma following a fall. His medical history was significant for heavy alcoholism since age 35 and related falls and injuries. Neurological examination demonstrated significant memory impairment, dysphasia, apraxia, agnosia and disturbance in executive functioning, leading to the diagnosis of alcoholic dementia. Computed tomography (CT) scan of his head repeated during 6 years demonstrated progressive central and peripheral brain atrophy with sulcal widening, ventricular enlargement, and cortical white matter shrinkage characteristic of chronic alcohol abuse [Figure 1, next page]. Long-standing heavy alcohol abuse leads to disproportionate loss of white matter with reduction in brain volume and brain weight.

The most commonly reported findings in the brains of alcoholics are sulcal widening and ventricular enlargement as well as cortical white matter shrinkage. The frontal lobes appear to be more vulnerable to alcohol- related brain damage than other cerebral regions. The cerebellum, cortical-limbic circuits, skeletal muscle, and peripheral nerves are also important targets of chronic alcohol-related metabolic injury and degeneration.. Although all cell types within the nervous system are vulnerable to the toxic, metabolic and degenerative effects of alcohol, astrocytes, oligodendrocytes and synaptic terminals are major targets, accounting for the white matter atrophy. A heavy drinking history is a cardinal feature in the criteria for alcoholic dementia, which include memory impairment in addition to one or more other cognitive symptoms. Among the cognitive symptoms are dysphasia, apraxia, agnosia, and disturbance in executive functioning. All these features were found in our patient and were persistent for at least 6 months of follow-up.

Alcohol abuse is a very serious health, social and economic problem worldwide. The present case conveys a clear message regarding the brain damage that results from chronic alcohol abuse.

https://www.ima.org.il/FilesUpload/IMAJ/0/172/86478.pdf

“A heavy drinking history is a cardinal feature in the criteria for alcoholic dementia, which include memory impairment in addition to one or more other cognitive symptoms. Among the cognitive symptoms are dysphasia, apraxia, agnosia, and disturbance in executive functioning.”

“Alcohol abuse is a very serious health, social and economic problem worldwide. The present case conveys a clear message regarding the brain damage that results from chronic alcohol abuse.”

“Prevalence of malnutrition is high in patients with cirrhosis. It is associated with increased complications and mortality.”

Journal Of Gastroenterology And Hepatology • October 2015

Malnutrition in cirrhosis increases morbidity and mortality

Author information

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Abstract

BACKGROUND AND AIMS

Malnutrition is frequent in patients with cirrhosis and is associated with complications like ascites, hepatic encephalopathy, infections, and death. We determined the prevalence of malnutrition by various methods and its clinical importance in patients with cirrhosis.

METHODS

Consecutive patients of cirrhosis from August 2013 to February 2015 were assessed. Nutritional status was assessed by traditional model (mid-arm circumference, triceps skinfold thickness, serum albumin, creatinine height index, total lymphocyte count), hand-grip, and body composition analysis measuring skeletal muscle mass and body fat mass. All patients were followed up for 12 months to assess the outcome.

RESULTS

247 patients (age 42.10±10.14 years, 81% male) were included in the study. Etiology of cirrhosis was alcohol in 53% patients. Prevalence of malnutrition was 59.5% according to traditional model, 66.8% by body composition analysis and 71.4% by hand-grip. Nutritional status was poor in alcoholic cirrhotics versus nonalcoholics as assessed by triceps skinfold thickness (9.33±2.9 vs 11.64±3.5 mm; P=0.001), serum albumin (25.1±4 vs 28.1±4 g/L; P=0.001), and body fat mass (7.6±3.1 vs 8.7±3.3 kg; P=0.008). Prevalence of malnutrition was 12/27 (44.5%), 96/131 (73.3%) and 84/89 (94.4%) in Child's class A, B, and C respectively. Complications requiring hospitalization (71.3% vs 38.2%; 0.002) and mortality (41.1% vs 18.2%; P=0.001) were more in malnourished patients compared to well nourished. Nutritional assessment parameters significantly correlated with the liver disease severity (P<0.05).

CONCLUSIONS

Prevalence of malnutrition is high in patients with cirrhosis. It is associated with increased complications and mortality.

http://www.ncbi.nlm.nih.gov/pubmed/25974421

“These data demonstrate that moderate maternal consumption of ethanol produces hyperactivity, enhances ethanol preference, and impairs learning and memory in guinea pig offspring.”

Behavioral Pharmacology • February 2012

Maternal ethanol consumption by pregnant guinea pigs causes neurobehavioral deficits and increases ethanol preference in offspring

Author information

Shea KM1, Hewitt AJ, Olmstead MC, Brien JF, Reynolds JN.

Division of Pharmacology and Toxicology, Department of Biomedical and Molecular Sciences, Queen’s University, Kingston, Ontario, Canada

Abstract

The objective of this study was to test the hypothesis that prenatal exposure to ethanol, through maternal consumption of an aqueous ethanol solution, induces neurobehavioral deficits and increases ethanol preference in offspring. Pregnant Dunkin-Hartley-strain guinea pigs were given 24-h access to an aqueous ethanol solution (5%, v/v) sweetened with sucralose (1 g/l), or water sweetened with sucralose (1 g/l), throughout gestation. Spontaneous locomotor activity was measured in the offspring on postnatal day (PD) 10. The offspring underwent either ethanol preference testing using a two-bottle-choice paradigm beginning on PD 40 or Morris water maze testing using a hidden moving platform design beginning on PD 60. Maternal consumption of a 5% (v/v) ethanol solution (average daily dose of 2.3±0.1 g of ethanol/kg maternal body weight; range: 1.8-2.8 g/kg) decreased offspring birth weight, increased spontaneous locomotor activity, and increased preference for an aqueous ethanol solution. In the Morris water maze test, sucralose-exposed offspring decreased escape latency on the second day of testing, whereas the ethanol-exposed offspring showed no improvement. These data demonstrate that moderate maternal consumption of ethanol produces hyperactivity, enhances ethanol preference, and impairs learning and memory in guinea pig offspring.

http://www.ncbi.nlm.nih.gov/pubmed/22157142

“Moderate alcohol consumption in a swine model of metabolic syndrome worsens glucose metabolism by altering activation of the insulin signaling pathway in the liver and skeletal muscle.”

Surgery • September 2012

Vodka and wine consumption in a swine model of metabolic syndrome alters insulin signaling pathways in the liver and skeletal muscle

Author information

Elmadhun NY1, Lassaletta AD, Chu LM, Bianchi C, Sellke FW.

Abstract

BACKGROUND

The purpose of this study was to examine the effects of alcohol in the context of metabolic syndrome on insulin signaling pathways in the liver and skeletal muscle.

METHODS

Twenty-six Yorkshire swine were fed a hypercaloric, high-fat diet for 4 weeks then split into 3 groups: hypercholesterolemic diet alone (HCC, n = 9), hypercholesterolemic diet with vodka (HCVOD, n = 9), and hypercholesterolemic diet with wine (HCW, n = 8) for 7 weeks. Animals underwent intravenous dextrose challenge before euthanasia and tissue collection.

RESULTS

HCC, HCVOD, and HCW groups had similar blood fasting glucose levels, liver function test, and body mass index. Thirty and 60 minutes after dextrose infusion, HCVOD and HCW groups had significantly increased blood glucose levels compared with the HCC group. The HCW group had significantly increased levels of insulin compared with the HCC group. Immunoblotting in skeletal muscle demonstrated that alcohol up-regulates p-IRS1, IRS2, AKT, AMPKa, PPARa, Fox01, and GLUT4. In the liver, HCW had up-regulation of AKT, AMPKa, and GLUT4 compared with HCC. Skeletal muscle immunohistochemistry demonstrated increased sarcolemmal expression of GLUT4 in both alcohol groups compared with HCC.

CONCLUSION

Moderate alcohol consumption in a swine model of metabolic syndrome worsens glucose metabolism by altering activation of the insulin signaling pathway in the liver and skeletal muscle.

Full text, photos, graphs, charts and 27 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3435558/

“This article shows the impact of high alcohol consumption on cardiovascular risk factors and reviews the literature on the associations between alcohol consumption and cardiovascular risk factors.”

Revue Medicale Suisse • March 2010

Association between alcohol consumption and cardiovascular risk factors: a narrative review

Author information

Foerster M1, Marques-Vidal P, Waeber G, Vollenweider P, Rodondi N.

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Abstract

Moderate alcohol consumption has been associated with lower coronary heart disease (CHD) risk. However, the impact of higher alcohol consumption on cardiovascular risk factors (CVRFs) is conflicting. We examined the association between alcohol consumption, CVRFs and the estimated 10-year CHD risk in the population-based CoLaus study in Lausanne, Switzerland. Among 5,769 participants without cardiovascular disease, 73% of the participants were alcohol drinkers; 16% consumed 14-34 drinks/week and 2% consumed > or = 35 drinks/week. This article shows the impact of high alcohol consumption on CVRFs and reviews the literature on the associations between alcohol consumption and CVRFs.

http://www.ncbi.nlm.nih.gov/pubmed/20373697

“Alcohol consumption promotes insulin sensitivity”

International Journal Of Obesity (London) • February 2009

Alcohol consumption promotes insulin sensitivity without affecting body fat levels

Author information

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Abstract

OBJECTIVE

Alcohol consumption promotes insulin sensitivity. In obesity, a decrease in body fat levels decreases the risk of developing insulin resistance; therefore, it is possible that alcohol improves insulin sensitivity by negatively affecting body fat. The aim of this study was to determine whether alcohol consumption promotes insulin sensitivity by reducing body fat levels in C57BL/6 male mice.

METHODS

We examined the effects of alcohol consumption on insulin sensitivity in male mice with three different body weight (BW) phenotypes. The BWs were induced by feeding the mice a 30% calorie-restricted (CR) regimen, a low-fat (LF) diet and a high-fat (HF) diet. The mice had free access to water or 20% ethanol in the drinking water. To determine the effects of the three different BW phenotypes and of alcohol on glucose regulation and insulin sensitivity, we performed the insulin tolerance test (ITT) and glucose tolerance test (GTT) on the mice. The effects of the diets and alcohol on body composition, percent body fat (% BF), percent lean mass and bone mineral density (BMD) were determined by dual-energy X-ray absorptiometry (DEXA).

RESULTS

Data show that mice with the highest body fat levels (HF) were insulin resistant and glucose intolerant. In contrast, mice with the lowest body fat levels (CR) were the most insulin sensitive and cleared the injected endogenous glucose the fastest. Results show that alcohol did not affect GTT in any of the BW phenotypes. However, alcohol consumption promoted insulin sensitivity in mice consuming both the LF and HF diets. Alcohol consumption increased insulin sensitivity without affecting body fat levels, as body fat levels were similar in mice consuming the LF or HF diets and drinking either water or alcohol.

CONCLUSIONS

Alcohol consumption promotes insulin sensitivity without affecting body fat levels in mice consuming LF and HF diets.

http://www.ncbi.nlm.nih.gov/pubmed/19125162

“Our analysis confirms previous research findings that moderate alcohol consumption is protective for type 2 diabetes in men and women.”

Diabetes Care • November 2009

Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis

Author information

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Abstract

OBJECTIVE

To clarify the dose-response relationship between alcohol consumption and type 2 diabetes.

RESEARCH DESIGN AND METHODS

A systematic computer-assisted and hand search was conducted to identify relevant articles with longitudinal design and quantitative measurement of alcohol consumption. Adjustment was made for the sick-quitter effect. We used fractional polynomials in a meta-regression to determine the dose-response relationships by sex and end point using lifetime abstainers as the reference group.

RESULTS

The search revealed 20 cohort studies that met our inclusion criteria. A U-shaped relationship was found for both sexes. Compared with lifetime abstainers, the relative risk (RR) for type 2 diabetes among men was most protective when consuming 22 g/day alcohol (RR 0.87 [95% CI 0.76-1.00]) and became deleterious at just over 60 g/day alcohol (1.01 [0.71-1.44]). Among women, consumption of 24 g/day alcohol was most protective (0.60 [0.52-0.69]) and became deleterious at about 50 g/day alcohol (1.02 [0.83-1.26]).

CONCLUSIONS

Our analysis confirms previous research findings that moderate alcohol consumption is protective for type 2 diabetes in men and women.

http://www.ncbi.nlm.nih.gov/pubmed/19875607

“The purpose of this study was to investigate the relationship between alcohol consumption and the prevalence of the metabolic syndrome (MetS), type 2 diabetes mellitus (DM), coronary heart disease (CHD), stroke, peripheral arterial disease (PAD), and overall cardiovascular disease (CVD) in a Mediterranean cohort. **Heavy drinking was associated with an increase in the prevalence of all of these disease states.**”

Angiology • December 2007

Association of drinking pattern and alcohol beverage type with the prevalence of metabolic syndrome, diabetes, coronary heart disease, stroke, and peripheral arterial disease in a Mediterranean cohort

Author information

Athyros VG1, Liberopoulos EN, Mikhailidis DP, Papageorgiou AA, Ganotakis ES, Tziomalos K, Kakafika AI, Karagiannis A, Lambropoulos S, Elisaf M.

Atherosclerosis and Metabolic Syndrome Units, Aristotelean University, Hippocration Hospital, Thessaloniki, Greece

Abstract

The purpose of this study was to investigate the relationship between alcohol consumption and the prevalence of the metabolic syndrome (MetS), type 2 diabetes mellitus (DM), coronary heart disease (CHD), stroke, peripheral arterial disease (PAD), and overall cardiovascular disease (CVD) in a Mediterranean cohort. It consisted of a cross-sectional analysis of a representative sample of Greek adults (n = 4,153) classified as never, occasional, mild, moderate, or heavy drinkers. Cases with overt CHD, stroke, or PAD were recorded. In our population, 17% were never, 23% occasional, 27% mild, 24% moderate, and 9% heavy drinkers. Moderate alcohol consumption was associated with a lower trend for the prevalence of the MetS (P = .0001), DM (P < .0001), CHD (P = .0002), PAD (P = .005), and overall CVD (P = .001) but not stroke compared with no alcohol use. Heavy drinking was associated with an increase in the prevalence of all of these disease states. Wine consumption was associated with a slightly better effect than beer or spirits consumption on the prevalence of total CVD, and beer consumption was associated with a better effect than spirits consumption. Alcohol intake was positively related with body weight, high-density lipoprotein cholesterol levels, and hypertension. Moderate alcohol consumption is associated with a lower prevalence of the MetS, DM, PAD, CHD, and overall CVD but not stroke compared with no alcohol use in a Mediterranean population. Heavy drinking was associated with an increase in the prevalence of all of these disease states. Advice on alcohol consumption should probably mainly aim at reducing heavy drinking.

http://www.ncbi.nlm.nih.gov/pubmed/18216378

Current Pharmaceutical Design • July 2006

Fetal alcohol syndrome: a cautionary note

By E.L. Abel

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eabel@wayne.edu

Abstract

“Fetal alcohol syndrome (FAS) is a pattern of anomalies occurring in children born to alcoholic women. The main features of this pattern are pre and/or postnatal growth retardation, characteristic facial abnormalities, and central nervous system dysfunction, including mental retardation. Since its clinical recognition in 1973 it has progressed from an unrecognized condition to a major public health concern with exaggerated and unfounded claims as to causality and impact. This review summarizes some of the basic facts about fetal alcohol syndrome with respect to terminology, prevalence, and mechanisms, in the context of exposure risk.”

http://www.ncbi.nlm.nih.gov/pubmed/16611132

“A deficiency in the essential nutrient thiamine resulting from chronic alcohol consumption is one factor underlying alcohol-induced brain damage.”

Alcohol Research & Health • July 2004

The Role of Thiamine Deficiency in Alcoholic Brain Disease

Peter R. Martin, M.D., Charles K. Singleton, Ph.D., and Susanne Hiller–Sturmhöfel, Ph.D.

Peter R. Martin, M.D., is professor of psychiatry and pharmacology at
Vanderbilt University School of Medicine and director of the Vanderbilt Addiction Center, Nashville, Tennessee.
Charles K. Singleton, Ph.D., is professor and chair in the Department of Biological Science, Vanderbilt University
Nashville, Tennessee. Susanne Hiller–Sturmhöfel, Ph.D., is a science editor for Alcohol Research & Health

Abstract

A deficiency in the essential nutrient thiamine resulting from chronic alcohol consumption is one factor underlying alcohol–induced brain damage. Thiamine is a helper molecule (i.e., a cofactor) required by three enzymes involved in two pathways of carbohydrate metabolism. Because intermediate products of these pathways are needed for the generation of other essential molecules in the cells (e.g., building blocks of proteins and DNA as well as brain chemicals), a reduction in thiamine can interfere with numerous cellular functions, leading to serious brain disorders, including Wernicke–Korsakoff syndrome, which is found predominantly in alcoholics. Chronic alcohol consumption can result in thiamine deficiency by causing inadequate nutritional thiamine intake, decreased absorption of thiamine from the gastrointestinal tract, and impaired thiamine utilization in the cells. People differ in their susceptibility to thiamine deficiency, however, and different brain regions also may be more or less sensitive to this condition.

This article describes the normal role of thiamine in brain functioning as well as the pathological consequences that result from thiamine deficiency. Specific actions of thiamine on a cellular level then are reviewed, followed by a discussion of how alcohol affects the body’s processing and availability of thiamine as well as thiamine utilization by the cells. Finally, the article explores the hypothesis that people may differ in their sensitivity to thiamine deficiency and that different brain regions may be more or less sensitive to a deficiency in this important nutrient. Thiamine deficiency is particularly important because it can exacerbate many of the other processes by which alcohol induces brain injury, as described in other articles in this issue of Alcohol Research & Health.

Full text with references

http://pubs.niaaa.nih.gov/publications/arh27-2/134-142.htm

“Alcoholic drinks are capable of triggering a wide range of allergic and allergic-like responses, including rhinitis, itching, facial swelling, headache, cough and asthma. The aetiology of wine-induced asthmatic responses may be complex and may involve several co-factors.”

Addiction Biology • March 2003

Allergic and asthmatic reactions to alcoholic drinks

Author information

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Abstract

Alcoholic drinks are capable of triggering a wide range of allergic and allergic-like responses, including rhinitis, itching, facial swelling, headache, cough and asthma. Limited epidemiological data suggests that many individuals are affected and that sensitivities occur to a variety of drinks, including wine, beer and spirits. In surveys of asthmatics, over 40% reported the triggering of allergic or allergic-like symptoms following alcoholic drink consumption and 30 - 35% reported worsening of their asthma. Sensitivity to ethanol itself can play a role in triggering adverse responses, particularly in Asians, which is due mainly to a reduced capacity to metabolize acetaldehyde. In Caucasians, specific non-alcohol components are the main cause of sensitivities to alcoholic drinks. Allergic sensitivities to specific components of beer, spirits and distilled liquors have been described. Wine is clearly the most commonly reported trigger for adverse responses. Sensitivities to wine appear to be due mainly to pharmacological intolerances to specific components, such as biogenic amines and the sulphite additives. Histamine in wine has been associated with the triggering of a wide spectrum of adverse symptoms, including sneezing, rhinitis, itching, flushing, headache and asthma. The sulphite additives in wine have been associated with triggering asthmatic responses. Clinical studies have confirmed sensitivities to the sulphites in wine in limited numbers of individuals, but the extent to which the sulphites contribute to wine sensitivity overall is not clear. The aetiology of wine-induced asthmatic responses may be complex and may involve several co-factors.

http://www.ncbi.nlm.nih.gov/pubmed/12745410

“In conclusion, unlike binge drinking, chronic moderate alcohol consumption appears to have a cardioprotective effect in the fasted state, an effect attenuated by the observed temporary postprandial hyperchylomicronemia and hypertriglyceridemia resulting from a direct effect of alcohol on CM size and number.”

Food And Chemical Toxicology • November 2003

Effect of acute and chronic moderate alcohol consumption on fasted and postprandial lipemia in the rat

Author information

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Abstract

Effects of acute and chronic alcohol intake on fasted and postprandial lipemia in the rat model are reported. In the acute study, fasted rats are loaded with a 30% w/w olive oil emulsion with or without 8% alcohol in the form of ethanol, beer or whisky. After 3 h, either mesenteric lymph or blood is collected and the TAG-rich lipoprotein fractions are isolated. In the chronic study, animals received, for a period of 10 weeks, 3% alcohol in drinking water in the form of ethanol, beer or whisky. Blood samples were collected from animals in either the fasted state or after being loaded with the fat load as described above. Alcohol ingestion along with a fat load increases the number (increased net apoB48 secretion) and reduces the size (reduced TAG/apoB48 ratio) of CM secreted into the mesenteric lymph duct. It also delays gastric emptying, reduces trans-enterocyte TAG flux rates and increases plasma concentrations of TAG, cholesterol and CM. Similar conditions also results in increased total phospholipid and cholesterol content of CM but not of VLDL, indicating an enhanced liver bile secretion into the gut; however, a significant increase in plasma VLDL concentration is observed. Unlike the acute study, an alcohol-fat load in animals put on chronic alcohol intake results in increased HDL cholesterol concentrations and less pronounced postprandial hypertriglyceridemia and hypercholesterolemia but not hyperchylomicronemia. In the fasted state, plasma TAG and total apoB concentrations are not modified in these animals, and an increase in HDL and a decrease in total and LDL cholesterol concentrations are observed. No liver function impairment is observed following the 10-week period of chronic alcohol intake. In conclusion, unlike binge drinking, chronic moderate alcohol consumption appears to have a cardioprotective effect in the fasted state, an effect attenuated by the observed temporary postprandial hyperchylomicronemia and hypertriglyceridemia resulting from a direct effect of alcohol on CM size and number.

http://www.ncbi.nlm.nih.gov/pubmed/12963008

“Inhibition and working memory deficits, associated with low levels of CBF in the medial frontal gyrus, are related to the difficulty of maintaining short-term abstinence from alcohol.”

Alcohol And Alcoholism • July 2002

Contribution of frontal cerebral blood flow measured by (99m)Tc-Bicisate spect and executive function deficits to predicting treatment outcome in alcohol-dependent patients

Author information

Noël X1, Sferrazza R, Van Der Linden M, Paternot J, Verhas M, Hanak C, Pelc I, Verbanck P.

Abstract

AIM

To determine whether inhibition and working memory deficits, and reduced regional cerebral blood flow (rCBF) (previously shown to be related), measured at the end of a detoxification programme, predict alcoholic relapse 2 months later.

METHODS

Twenty uncomplicated alcoholic inpatients were investigated at the end of detoxification, at least 7 days since the last dose of diazepam, and a mean of 18.8 days since the last drink. Their performance was assessed on the inhibition (Hayling) test, working memory (Alpha-span task), episodic memory (California Verbal Learning Test) and abstract reasoning (Progressive Matrices). Frontal CBF was assessed at the same time with a semiquantitative (99m)Tc-Bicisate SPECT procedure. Patients were contacted 2 months later. Patients who abstained (n = 9) did not differ from those who relapsed (n = 11) on age, gender, smoking, duration of alcohol misuse, number of previous detoxifications, amount of ethanol consumed the month prior to admission to the detoxification programme, state anxiety, trait anxiety, or depression.

RESULTS

Relapsed subjects had shown a lower uptake of (99m)Tc-Bicisate in the bilateral medial frontal gyrus (n = 9; mean ratio +/- SD = 0.69 +/- 0.006) than abstainers (n = 11; 0.85 +/- 0.19), and poorer performance on the Alpha-span task and the Hayling test. The other tests were not different.

CONCLUSIONS

Inhibition and working memory deficits, associated with low levels of CBF in the medial frontal gyrus, are related to the difficulty of maintaining short-term abstinence from alcohol.

Link to Full text

http://www.ncbi.nlm.nih.gov/pubmed/11093969

“These results indicate that the Bergmann glial fibers are the GFAP-expressing structures of the cerebellum most sensitive to moderate-to-heavy chronic ethanol exposure and that this effect is dose dependent.”

Alcohol • January 2001

Dose-dependent decrease in glial fibrillary acidic protein-immunoreactivity in rat cerebellum after lifelong ethanol consumption

Author information

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Abstract

The effects of aging and lifelong ethanol consumption on astrocytic morphology and glial fibrillary acidic protein-immunoreactivity (GFAP-IR) in the cerebellar vermis obtained from ethanol-preferring Alko, Alcohol (AA) rats were analyzed by using computer-assisted image analysis. The ethanol-consuming animals (both male and female) were given ethanol (10%-12%, vol./vol.) as the only available fluid for 21 months (3-24 months), whereas the young (3 months) and the old (24 months) controls received water. In the male rats, but not in the female rats, an age-related decrease in GFAP-IR was found in folia II, VII, and X of the molecular layer, and in turn, an age-related increase was found in folium X of the granular layer, indicating opposite changes in GFAP-IR for male rats due to aging in adjacent brain regions. In the female rats, 21 months of daily average ethanol consumption of 6.6 g/kg resulted in decreased GFAP-IR in folium VII of the molecular layer, and the decrease in cerebellar GFAP-IR correlated with the average daily ethanol intake (r=-.886, P=.019) when folia II, IV, VII, and X were analyzed together. No effect of ethanol on GFAP-IR was detected in the granular layer or in the central white matter of the female rats. There was no change in GFAP-IR in any of the three cerebellar layers of the male rats with average daily ethanol consumption of 3.2 g/kg. These results indicate that the Bergmann glial fibers are the GFAP-expressing structures of the cerebellum most sensitive to moderate-to-heavy chronic ethanol exposure and that this effect is dose dependent.

http://www.ncbi.nlm.nih.gov/pubmed/11282445

“This article represents ... A close association between testicular atrophy, muscle atrophy, and the increase in protein catabolism after chronic ethanol administration ...”

Alcoholism, Clinical And Experimental Research • May 2001

Recent advances in the pathology of alcoholic myopathy

Author information

Preedy VR1, Adachi J, Peters TJ, Worrall S, Parkkila S, Niemela O, Asamo M, Ueno Y, Takeda K, Yamauchi M, Sakamoto K, Takagi M, Nakajima H, Toda G.

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Abstract

This article represents the proceedings of a symposium at the 2000 ISBRA Meeting in Yokohama, Japan. The chairs were Victor R. Preedy and Junko Adachi. The presentations were (1) Alcoholic myopathy: Past, present and future, by Timothy J. Peters and Victor R. Preedy; (2) Protein adducts in the type I and II fiber-predominant muscles of the ethanol-fed rat, by Simon Worrall, Seppo Parkkila, and Onni Niemela; (3) Hydroperoxides and changes in alcoholic myopathy, by Junko Adachi, Migiwa Asamo, and Yasuhino Ueno; and (4) A close association between testicular atrophy, muscle atrophy, and the increase in protein catabolism after chronic ethanol administration, by Kunihiko Takeda, Masayoshi Yamauchi, Kazuhiko Sakamoto, Masaru Takagi, Hisato Nakajima, and Gotaro Toda.

http://www.ncbi.nlm.nih.gov/pubmed/11391050

Pediatrics • August 2001

Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect

Author information

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Abstract

OBJECTIVE

Moderate to heavy levels of prenatal alcohol exposure have been associated with alterations in child behavior, but limited data are available on adverse effects after low levels of exposure. The objective of this study was to evaluate the dose-response effect of prenatal alcohol exposure for adverse child behavior outcomes at 6 to 7 years of age.

METHODS

Beginning in 1986, women attending the urban university-based maternity clinic were routinely screened at their first prenatal visit for alcohol and drug use by trained research assistants from the Fetal Alcohol Research Center. All women reporting alcohol consumption at conception of at least 0.5 oz absolute alcohol/day and a 5% random sample of lower level drinkers and abstainers were invited to participate to be able to identify the associations between alcohol intake and child development. Maternal alcohol, cigarette, and illicit drug use were prospectively assessed during pregnancy and postnatally. The independent variable in this study, prenatal alcohol exposure, was computed as the average absolute alcohol intake (oz) per day across pregnancy. At each prenatal visit, mothers were interviewed about alcohol use during the previous 2 weeks. Quantities and types of alcohol consumed were converted to fluid ounces of absolute alcohol and averaged across visits to generate a summary measure of alcohol exposure throughout pregnancy. Alcohol was initially used as a dichotomous variable comparing children with no prenatal alcohol exposure to children with any exposure. To evaluate the effects of different levels of exposure, the average absolute alcohol intake was relatively arbitrarily categorized into no, low (>0 but <0.3 fl oz of absolute alcohol/day), and moderate/heavy (>/=0.3 fl oz of absolute alcohol/day) for the purpose of this study. Six years later, 665 families were contacted. Ninety-four percent agreed to testing. Exclusions included children who missed multiple test appointments, had major congenital malformations (other than fetal alcohol syndrome), possessed an IQ >2 standard deviations from the sample mean, or had incomplete data. The Achenbach Child Behavior Checklist (CBCL) was used to assess child behavior. The CBCL is a parent questionnaire applicable to children ages 4 to 16 years. It is widely used in the clinical assessment of children's behavior problems and has been extensively used in research. Eight syndrome scales are further grouped into Externalizing or undercontrolled (Aggressive and Delinquent) behavior and Internalizing or overcontrolled (Anxious/Depressed, Somatic Complaints, and Withdrawn) behaviors. Three syndromes (Social, Thought, and Attention Problems) fit neither group. Higher scores are associated with more problem behaviors. Research assistants who were trained and blinded to exposure status independently interviewed the child and caretaker. Data were collected on a broad range of control variables known to influence childhood behavior and/or to be associated with prenatal alcohol exposure. These included perinatal factors of maternal age, education, cigarette, cocaine, and other substances of abuse and the gestational age of the baby. Postnatal factors studied included maternal psychopathology, continuing alcohol and drug use, family structure, socioeconomic status, children's whole blood lead level, and exposure to violence. Data were collected only from black women as there was inadequate representation of other racial groups.

STATISTICAL ANALYSES

Statistical analyses were performed using the SPSS statistical package. Frequency distribution, cross-tabulation, odds ratio, and chi(2) tests were used for analyzing categorical data. Continuous data were analyzed using t tests, analyses of variance (ANOVAs) with posthoc tests, and regression analysis.

RESULTS

Testing was available for 501 parent-children dyads. Almost one fourth of the women denied alcohol use during pregnancy. Low levels of alcohol use were reported in 63.8% and moderate/heavy use in 13% of pregnancies. Increasing prenatal alcohol exposure was associated with lower birth weight and gestational age, higher lead levels, higher maternal age, and lower education level, prenatal exposure to cocaine and smoking, custody changes, lower socioeconomic status, and paternal drinking and drug use at the time of pregnancy. Children with any prenatal alcohol exposure were more likely to have higher CBCL scores on Externalizing (Aggressive and Delinquent) and Internalizing (Anxious/Depressed and Withdrawn) syndrome scales and the Total Problem Score. The odds ratio of scoring in the clinical range for Delinquent behavior was 3.2 (1.3-7.6) in children with any prenatal exposure to alcohol compared with nonexposed controls. The threshold dose was evaluated with the 3 prenatal alcohol exposure groups. One-way ANOVA revealed a significant between group difference for Externalizing (Aggressive and Delinquent) and the Total Problem Score.

http://www.ncbi.nlm.nih.gov/pubmed/11483844

Alcohol And Alcoholism • November 2000

Mechanisms of hyponatraemia in alcohol patients

Author information

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Abstract

“Hyponatraemia is commonly reported in chronic alcoholic patients. However, the underlying pathogenetic mechanisms are not well delineated. In the current study, we analysed the possible pathophysiological mechanisms of hyponatraemia in a group of alcoholic patients (n = 127) admitted to our hospital for causes related to alcohol misuse. Hyponatraemia (serum sodium <134 mmol/l) was found in 22 patients (17.3%). The most common cause of hyponatraemia in our cohort was hypovolaemia (12 patients); pseudohyponatraemia was diagnosed in six patients with alcohol-induced severe hypertriglyceridaemia. It is of interest that two patients fulfilled the criteria of the so-called ‘beer potomania’ syndrome, while in two others, hyponatraemia was due to reset osmostat or to cerebral salt wasting syndrome, not previously described in alcoholic patients. It is concluded that hyponatraemia is a frequently observed electrolyte disorder in hospitalized alcoholic patients and is related to various pathophysiological mechanisms.”

http://www.ncbi.nlm.nih.gov/pubmed/11093969

American Journal Of Preventive Medicine • August 1999

Alcohol use prior to pregnancy recognition

Author information

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Abstract

BACKGROUND

Frequent alcohol use during the first 8 weeks of pregnancy can result in spontaneous abortion and dysmorphologic changes in the developing organ systems of the embryo, including the heart, kidneys, and brain. However, few population-based studies are available that describe the prevalence of frequent drinking (6 or more drinks per week) among women prior to and during early pregnancy (the periconceptional period), and the sociodemographic and behavioral factors that characterize these women. Such knowledge is fundamental to the design of targeted interventions for the prevention of fetal alcohol syndrome (FAS) and other prenatal alcohol-related disorders.

METHODS

This cross-sectional study used survey data collected by the National Center for Health Statistics as part of the 1988 National Maternal and Infant Health Survey (NMIHS). Weighted prevalence estimates were calculated using SUDAAN, and multivariate analyses were used to determine risk factors for frequent drinking.

RESULTS

Forty-five percent of all women surveyed reported consuming alcohol during the 3 months before finding out they were pregnant, and 5% reported consuming 6 or more drinks per week. Sixty percent of women who reported alcohol consumption also reported that they did not learn they were pregnant until after the fourth week of gestation. Risk factors for frequent drinking during the periconceptional period included 1 or more of the following: being unmarried, being a smoker, being white non-Hispanic, being 25 years of age or older, or being college educated.

CONCLUSIONS

Half of all pregnant women in this study drank alcohol during the 3 months preceding pregnancy recognition, with 1 in 20 drinking at moderate to heavy levels. The majority did not know they were pregnant until after the fourth week of pregnancy, and many did not know until after the 6th week. Alcohol is a teratogen capable of producing a number of adverse reproductive and infant outcomes. Public health measures needed to reduce these potentially harmful exposures include alcohol assessment, education, and counseling for women of childbearing age, with referral sources for problem drinking, and family planning services for pregnancy postponement until problem drinking is resolved.

http://www.ncbi.nlm.nih.gov/pubmed/10490051

“[This is] an important model for further research on ethanol-induced pathological changes in the central nervous system.”

Alcoholism, Clinical And Experimental Research • April 1997

Effects of lifelong ethanol consumption on cerebellar layer volumes in AA and ANA rats

Author information

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Abstract

Aging and chronic alcohol consumption can cause degenerative changes in the cerebellar cortex. In this study, the effects of aging and lifelong alcohol consumption on cerebellar cortical layer volumes (molecular and granular) and also white matter layer volumes were studied in alcohol-preferring (AA) and nonpreferring (ANA) rats of both sexes. The ethanol-consuming animals (EtOH) had 12% (w/v) ethanol as the only available fluid from 4 to 22 months of age, whereas the young (3 month) and old controls (24 months) had only water to drink. The volumes of molecular, granular, and white matter layers of the cerebellar vermis in folia II, IV, VII, and X were measured by using systematic sampling and a point-counting method. The volumes of the granular and white matter layers showed consistent increase between 3 and 24 months of age, whereas the volume of the molecular layer remained unchanged with increasing age. Individual ethanol intake was measured over a 1-week period at the beginning and at the end of chronic ethanol exposure. Significant (ANOVA, $p = 0.000$) sex difference was found in the drinking behavior in both lines, with females consuming more alcohol than males (daily ethanol consumption at 22 months of age 3.2 +/- 0.3 vs. 7.1 +/- 0.3 g/kg for AA males and females; 3.2 +/- 0.3 vs. 5.4 +/- 0.4 g/kg for ANA males and females, respectively). The only ethanol-induced effect on the cerebellum was observed in ANA-EtOH females with a 15% reduction in the volumes of the molecular and granular layer in folium II compared with age-matched controls and a significant ($p < 0.05$, analysis of covariance with ethanol intake as a covariate) line difference in folium II (molecular and granular layers) was observed between ANA-EtOH females and AA-EtOH females. Furthermore, the volume of the molecular layer in folium II was significantly ($p < 0.05$, analysis of covariance with ethanol intake and body weights as covariates) reduced for ANA-EtOH females, compared with ANA-EtOH males indicating a sex difference in the cerebellar degeneration due to chronic alcohol consumption. Of the three layers studied, the white matter layer was the most resistant layer to the effects caused by chronic alcohol consumption. In view of the fact that AA and ANA rats of both sexes differ regarding the drinking behavior and ethanol metabolism, they provide an important model for further research on ethanol-induced pathological changes in the central nervous system.

http://www.ncbi.nlm.nih.gov/pubmed/9113269

“In conclusion, asymptomatic chronic alcoholics frequently showed reversible frontal lobe hypoperfusion, which is related to recent ethanol intake, reflects brain function impairment and is independent of brain atrophy.”

Journal Of Nuclear Medicine • September 1993

Regional cerebral blood flow-SPECT in chronic alcoholism: relation to neuropsychological testing

Author information

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Abstract

To determine the prevalence of central nervous system damage due to ethanol, we evaluated 40 asymptomatic chronic alcoholics and 20 age-matched controls. Studies included neuropsychological testing, brain 99mTc-HMPAO SPECT, and morphometric analysis by CT scan. In the qualitative analysis, 30 of the 40 alcoholics showed hypoperfused areas on SPECT scan. In the semiquantitative analysis, alcoholics exhibited significant reduction in regional cerebral blood flow (rCBF) ratio of all brain lobes compared to controls ($p < 0.001$). The rCBF ratio was mainly reduced in frontal lobes (65%). Only 11 alcoholics showed significant frontal lobe atrophy in the morphometric analysis; most also had abnormalities on SPECT scan. Alcoholics exhibited significant impairment of frontal tasks and visuospatial skills. Frontal test impairment was independently related to both frontal atrophy and hypoperfusion. In a group of ten alcoholics in whom another SPECT scan was performed after 2 mo of ethanol abstinence, rCBF ratio of the frontal lobes normalized in eight, without frontal atrophy. In patients without frontal atrophy, reduced rCBF ratio of the anterior portion of the frontal lobes correlated negatively with frontal test results ($r = -0.6535$, $p < 0.001$). A significant negative correlation between cerebral perfusion and the amount of ethanol consumed in the month prior to study was observed ($r = -0.6289$, $p < 0.001$). In conclusion, asymptomatic chronic alcoholics frequently showed reversible frontal lobe hypoperfusion, which is related to recent ethanol intake, reflects brain function impairment and is independent of brain atrophy.

Link to Full text

http://www.ncbi.nlm.nih.gov/pubmed/8355063

“A large number of congenital disorders are due to alcohol consumption during pregnancy. Data available on this subject is very important and leaves no doubt in the disastrous effects of prenatal alcohol intake. Babies born with fetal alcohol syndrome present constant characteristics such as pre and post natal growth retardation, cranio-facial dysmorphism and central nervous system abnormalities.”

Journal Of Toxicology And Clinical Experimentation • March 1990

Alcohol and pregnancy: what is the level of risk?

Author information

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Abstract

A large number of congenital disorders are due to alcohol consumption during pregnancy. These anomalies are also known as the “fetal alcohol syndrome”. Data available on this subject is very important and leaves no doubt in the disastrous effects of prenatal alcohol intake. Babies born with fetal alcohol syndrome present constant characteristics such as pre and post natal growth retardation, cranio-facial dysmorphism and central nervous system abnormalities. The mechanism by which alcohol produces these defects are linked to: 1. The alteration of essential aminoacid transfer. 2. Fetal hypoxia. 3. Central nervous system cellular proliferation and differentiation inhibition (mainly in the cerebellum and hippocampus). 4. Auto-immune reaction to S-100 protein. 5. Hormonal dysfunction. 6. Postnatal inhibition of response to growth hormones. The major risk is undoubtfully the excessive daily alcohol intake (2-6 consumptions/day). Social type of alcohol consumption brings more discrete effects and often these happen much later. Low birth weight and mental retardation may be seen with the absorption of 15 ml of alcohol per day (1 beer or 1 glass of wine or 40 ml of liquor) 52 mg/100 ml of blood alcohol has been identified as the fetal threshold activity concentration, while 140 mg/100 ml is associated with evident teratogenicity. Other factors such as maternal age and genetic predisposition also add to the risks of prenatal alcohol exposure.

http://www.ncbi.nlm.nih.gov/pubmed/2201763

“Central nervous system dysfunction includes mental retardation, the most serious consequence of in utero alcohol exposure, hyperactivity, sleep disorders and miscellaneous behavioral difficulties. If only one or two of these broad characteristics are present and the mother is suspected of drinking during pregnancy, then a diagnosis of ‘possible fetal alcohol syndrome,’ or ‘partial fetal alcohol syndrome,’ or ‘fetal alcohol effects,’ or ‘alcohol-related birth defects’ may be made.”

Drug & Alcohol Dependence • September 1984

Prenatal effects of alcohol

By E.L. Abel

Abstract

Suspicion of alcohol’s teratogenic potential stretches back many centuries, but it is only recently that solid support for this possibility has been produced. There is now little doubt that alcohol can produce developmental defects, but there are many questions that still remain to be answered concerning the impact of alcohol on the conceptus. One major question that remains to be resolved is why only a small percentage of alcoholic women give birth to children with Fetal Alcohol Syndrome (FAS), whereas other alcoholic women who drink the same amount do not. Another important issue concerns the way in which alcohol produces its effects. Although one of the most likely ways in which alcohol’s teratogenic actions are mediated appears to be via hypoxia, other mechanisms such as direct toxicity of alcohol or acetaldehyde may be involved. FAS refers to a pattern of defects in children born to alcoholic women. For a diagnosis of FAS to be made, the patient must have three main characteristics: (1) pre- and postnatal growth retardation (greater than or equal to 2 S.D. for length and weight), (2) facial anomalies, and (3) central nervous system dysfunction Pre- and postnatal growth retardation are the most reliable consequences of fetal alcohol exposure. In many cases, patients with the syndrome weigh less than 2500 g at birth and most do not exhibit postnatal ‘catch-up growth’ Among the distinctive facial anomalies seen in conjunction with the syndrome are absent-to-indistinct philtrum, epicanthic folds, thin upper lip and short upturned nose. Joint, limb and cardiac anomalies are also often present. Central nervous system dysfunction includes mental retardation, the most serious consequence of in utero alcohol exposure, hyperactivity, sleep disorders and miscellaneous behavioral difficulties. If only one or two of these broad characteristics are present and the mother is suspected of drinking during pregnancy, then a diagnosis of ‘possible fetal alcohol syndrome,’ or ‘partial fetal alcohol syndrome,’ or ‘fetal alcohol effects,’ or ‘alcohol-related birth defects’ may be made. However, without evidence of maternal drinking during pregnancy, this diagnosis is very tentative, since many of these effects are also observed in conjunction with many other congenital disorders.

http://www.ncbi.nlm.nih.gov/pubmed/6386408

It's 6 pm and it's been a long day... 1 Unit of alcohol consumed

BRAIN

From the first sip, alcohol is absorbed into the bloodstream and reaches the brain. Although you won't be aware of it, there is an impairment of brain function, which deteriorates further the more you drink. Cognitive abilities that are acquired later in life, such as conduct and behaviour, are the first to go. Early on you will experience mild euphoria and loss of inhibition, as alcohol impairs regions of the brain controlling behaviour and emotion. Most vulnerable are the brain cells associated with memory, attention, sleep and coordination. Sheer lack of mass means that people who weigh less become intoxicated more quickly, and women will feel the effects faster than men. This is also because their bodies have lower levels of water.

HEART

Your pulse quickens after just one unit. Alcohol is a vasodilator - it makes the peripheral blood vessels relax to allow more blood to flow through the skin and tissues, which results in a drop in blood pressure. In order to maintain sufficient blood flow to the organs, the heart rate increases. Your breathing rate may also speed up.

8 pm • Five Units of alcohol consumed

DIGESTIVE SYSTEM

The Government advises men to drink no more than three to four units a day and women no more than two to three, so after two pints of normal-strength beer (four units) or a large glass of red wine (3.5 units) we have already exceeded our healthy guidelines. The alcohol is absorbed through the stomach and small intestine and if you are not used to it, even small amounts of alcohol can irritate the stomach lining. This volume of alcohol also begins to block absorption of essential vitamins and minerals.

SKIN

Alcohol increases bloodflow to the skin, making you feel warm and look flushed. It also dehydrates, increasing the appearance of fine lines. According to Dr Nicholas Perricone, a dermatologist, even five units will lead to an unhealthy appearance for days.

11 pm • 10 Units of alcohol consumed

LUNGS

A small amount of alcohol speeds up the breathing rate. But at this level of intoxication, the stimulating effects of alcohol are replaced by an anaesthetic effect that acts as a depressant on the central nervous system. The heart rate lowers, as does blood pressure and respiration rates, possibly to risky levels - in extreme cases the effect could be fatal. During exhalation, the lungs excrete about 5 per cent of the alcohol you have consumed - it is this effect that forms the basis for the breathalyser test.

1 am • 15 Units of alcohol consumed

LIVER

Alcohol is metabolized in the liver and excessive alcohol use can lead to acute and chronic liver disease. As the liver breaks down alcohol, by-products such as acetaldehyde are formed, some of which are more toxic to the body than alcohol itself. It is these that can eventually attack the liver and cause cirrhosis. A heavy night of drinking upsets both the delicate balance of enzymes in the liver and fat metabolism. Over time, this can lead to the development of fatty globules that cause the organ to swell. It is generally accepted that drinking more than seven units (men) and five units (women) a day will raise the risk of liver cirrhosis.

3 am • 20 Units of alcohol consumed

HEART

More than 35 units a week, or a large number in one sitting, can cause 'holiday heart syndrome'. This is atrial fibrillation - a rapid, irregular heartbeat that happens when the heart's upper chambers contract too quickly. As a result, the heartbeat is less effective at pumping blood from the heart, and blood may pool and form clots. These can travel to the brain and cause a stroke. Atrial fibrillation gives a person nearly a fivefold increased risk of stroke. The effect is temporary, provided heavy drinking is stopped.

BLOOD

By this stage, alcohol has been carried to all parts of the body, including the brain, where it dissolves into the water inside cells. The effect of alcohol on the body is similar to that of an anaesthetic - by this stage, inhibitions are lost and feelings of aggression will surge.

When You Finally Wake Up The Following Day ... BRAIN

Alcohol dehydrates virtually every part of the body, and is also a neurotoxin that causes brain cells to become damaged and swell. This causes the hangover and, combined with low blood-sugar levels, can leave you feeling awful. Cognitive abilities such as concentration, coordination and memory may be affected for several days.

DIGESTION

Generally, it takes as many hours as the number of drinks you have consumed to burn up all the alcohol. Feelings of nausea result from dehydration, which also causes your thumping headache.

KIDNEYS

Alcohol promotes the making of urine in excess of the volume you have drunk and this can cause dehydration unless extra fluid is taken. Alcohol causes no damage or harm to the kidneys in the short term, but your kidneys will be working hard.

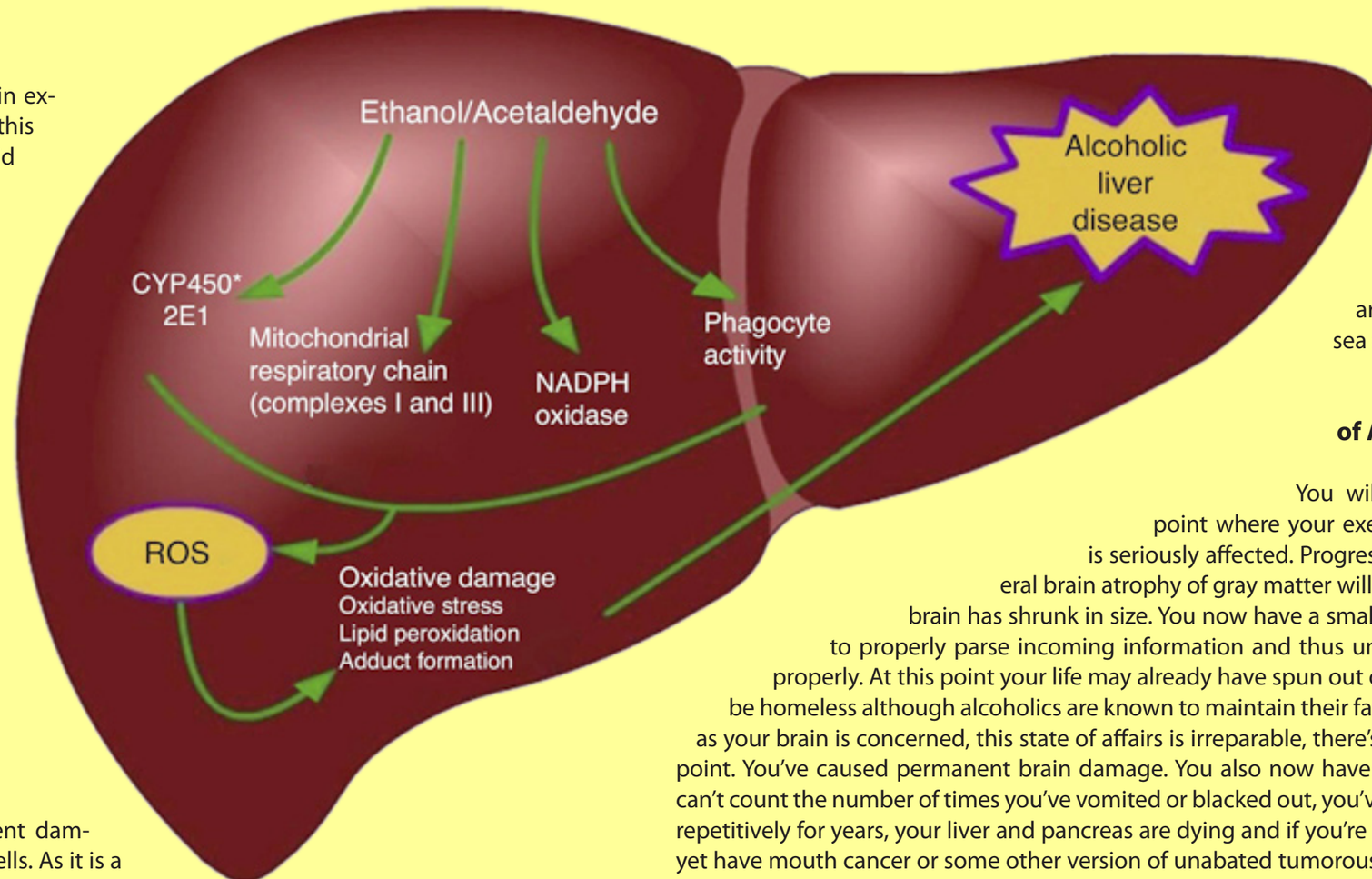
One Year Later ...

REPRODUCTIVE ORGANS

Heavy drinking causes a drop in testosterone levels in men, and causes testicular shrinkage and impotence. In females, menstrual cycles can be disrupted and fertility is affected. Studies have shown that women who drink up to five units of alcohol a week are twice as likely to conceive as those who drink 10 or more. It is thought it may affect the ability of the fertilized egg to implant.

BRAIN

Over time, alcohol can cause permanent damage to the connection between nerve cells. As it is a depressant, alcohol can trigger episodes of depression, anxiety and lethargy.



HEART

Small amounts of alcohol (no more than a unit a day) can protect the heart, but heavy drinking leads to chronic high blood pressure and other heart irregularities.

BLOOD

Alcohol kills the oxygen-carrying red blood cells, which can lead to anaemia.

CANCER

Excessive alcohol consumption is linked to an increase in the risk of most cancers. Mid-2016, Cancer Research UK warned how growing alcohol use is causing a steep rise in mouth cancer.

PANCREAS

Just a few weeks of heavy drinking can result in painful inflammation of the pancreas, known as pancreatitis. It results in a swollen abdominal area and can cause nausea and vomiting.

After 6 Years of Alcohol Abuse

You will now have reached a point where your executive decision making is seriously affected. Progressive central and peripheral brain atrophy of gray matter will have occurred and your brain has shrunk in size. You now have a smaller brain and are unable to properly parse incoming information and thus unable to make decisions properly. At this point your life may already have spun out of control and you could be homeless although alcoholics are known to maintain their facades for decades. As far as your brain is concerned, this state of affairs is irreparable, there's no coming back at this point. You've caused permanent brain damage. You also now have heart irregularities, you can't count the number of times you've vomited or blacked out, you've dehydrated your body repetitively for years, your liver and pancreas are dying and if you're the lucky sort, you don't yet have mouth cancer or some other version of unabated tumorous growth. Live hard. Your life will be short.

CHAPTER THIRTY-THREE

Air

The Peer Review

Air is by far the cheapest food additive and the least recognized, but it's perfectly safe. You pay for air purposely injected into various foods. Extruded snack foods such as breakfast cereals like Kix, Fruit Loops or even Cheerios, and inexpensive ice creams are fluffed out with air. In the ice cream world, the amount of air whipped into the final product is called 'overrun'.

Ben & Jerry's and Häagen-Dazs vanilla ice creams weigh more than 100 grams per half cup (120 grams), so they contain roughly 20% air. Breyers vanilla ice cream weighs 67 grams per half cup, with about 45% of the volume being air. That's one reason why the premium ice creams are higher in calories—they contain more actual ice cream per serving—and why the cheaper (and lower-calorie) ice creams are, well, cheaper. You're buying air. And generally a host of chemicals, sweeteners, emulsifiers and colorings. How much does your favorite ice cream weigh per cup?

Air is a component of most processed foods, frozen pre-cooked meals, carbonated drinks and other products. It's probably the safest additive but it's also very likely the cheapest additive used by the manufacturer and the single most expensive additive being sold back to the consumer. This chapter is a little light on peer reviewed reports and studies since there really wouldn't be many regarding the safety of air as an additive to food. We're all breathing the same polluted air anyway. Included in this chapter then are just a few surprising reports and studies on inner city air and how it relates to cognitive dysfunction and neurological disorders. Since many of us live in and are raising children in or near the larger cities and because many of us work in these same cities, the few well researched reports in this chapter should be helpful. The air may not be fit to breathe but what choice is there? As a result of pollution our bodies sustain daily damage from the air we breathe, the water we drink and the dust we're surrounded by. All the more reason to become proactive where food drugs are concerned and eliminate them from your diet.

“Higher copper exposure was associated with poorer motor performance and altered structure of the basal ganglia ... the architecture of the ... region was less complete in terms of ... tissue composition ... The results establish an association between environmental copper exposure in children and alterations of basal ganglia structure and function.”

Abstract

INTRODUCTION

Children are more vulnerable to the effects of environmental elements. A variety of air pollutants are among the identified factors causing neural damage at toxic concentrations. It is not obvious, however, to what extent the tolerated high levels of air pollutants are able to alter brain development. We have specifically investigated the neurotoxic effects of airborne copper exposure in school environments.

METHODS

Speed and consistency of motor response were assessed in 2836 children aged from 8 to 12 years. Anatomical MRI, diffusion tensor imaging, and functional MRI were used to directly test the brain repercussions in a subgroup of 263 children.

RESULTS

Higher copper exposure was associated with poorer motor performance and altered structure of the basal ganglia. Specifically, the architecture of the caudate nucleus region was less complete in terms of both tissue composition and neural track water diffusion. Functional MRI consistently showed a reciprocal connectivity reduction between the caudate nucleus and the frontal cortex.

CONCLUSIONS

The results establish an association between environmental copper exposure in children and alterations of basal ganglia structure and function.

Full text, MRI Images, graphs, charts and 49 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4842931/

Brain Behavior • April 2016

Airborne copper exposure in school environments associated with poorer motor performance and altered basal ganglia

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Pujol J1, Fenoll R2, Macià D2, Martínez-Vilavella G2, Alvarez-Pedrerol M3, Rivas I4, Forns J3, Deus J5, Blanco-Hinojo L2, Querol X6, Sunyer J7.

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> “In conclusion, urban air pollution appears to adversely affect brain maturation in a critical age with changes specifically concerning the functional domain.”

Neuroimage • April 2016

Traffic pollution exposure is associated with altered brain connectivity in school children

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Abstract

Children are more vulnerable to the effects of environmental elements due to their active developmental processes. Exposure to urban air pollution has been associated with poorer cognitive performance, which is thought to be a result of direct interference with brain maturation. We aimed to assess the extent of such potential effects of urban pollution on child brain maturation using general indicators of vehicle exhaust measured in the school environment and a comprehensive imaging evaluation. A group of 263 children, aged 8 to 12years, underwent MRI to quantify regional brain volumes, tissue composition, myelination, cortical thickness, neural tract architecture, membrane metabolites, functional connectivity in major neural networks and activation/deactivation dynamics during a sensory task. A combined measurement of elemental carbon and NO2 was used as a putative marker of vehicle exhaust. Air pollution exposure was associated with brain changes of a functional nature, with no evident effect on brain anatomy, structure or membrane metabolites. Specifically, a higher content of pollutants was associated with lower functional integration and segregation in key brain networks relevant to both inner mental processes (the default mode network) and stimulus-driven mental operations. Age and performance (motor response speed) both showed the opposite effect to that of pollution, thus indicating that higher exposure is associated with slower brain maturation. In conclusion, urban air pollution appears to adversely affect brain maturation in a critical age with changes specifically concerning the functional domain.

http://www.ncbi.nlm.nih.gov/pubmed/26825441

Environmental Health Perspectives • June 2016

Urban and Transport Planning Related Exposures and Mortality: A Health Impact Assessment for Cities

Author information

Mueller N1,2,3, Rojas-Rueda D1,2,3, Basagaña X1,2,3, Cirach M1,2,3, Cole-Hunter T1,2,3, Dadvand P1,2,3, Donaire-Gonzalez D1,2,3,4, Foraster M5,6, Gascon M1,2,3, Martinez D1,2,3, Tonne C1,2,3, Triguero-Mas M1,2,3, Valentín A1,2,3, Nieuwenhuijsen M1,2,3.

Abstract

BACKGROUND

By 2050, almost 70% of people globally are projected to live in urban areas. As the environments we inhabit affect our health, urban and transport designs that promote healthy living are needed.

OBJECTIVE

We estimated the number of premature deaths preventable under compliance with international exposure recommendations for physical activity (PA), air pollution, noise, heat, and access to green spaces.

METHODS

We developed and applied the Urban and TranspOrt Planning Health Impact Assessment (UTOPHIA) tool to Barcelona. Exposure estimates and mortality data were available for 1357361 residents. We compared recommended with current exposure levels. We quantified the associations between exposures and mortality and calculated population attributable fractions to estimate the number of premature deaths preventable. We also modeled life-expectancy and economic impacts.

RESULTS

We estimated that annually almost 20% of mortality could be prevented if international recommendations for performance of PA, exposure to air pollution, noise, heat, and access to green space were complied with. Estimations showed that the biggest share in preventable deaths was attributable to increases in PA, followed by exposure reductions in air pollution, traffic noise and heat. Access to green spaces had smaller effects on mortality. Compliance was estimated to increase the average life expectancy by 360 (95% CI: 219, 493) days and result in economic savings of 9.3 (95% CI: 4.9; 13.2) billion € per year.

CONCLUSIONS

PA factors and environmental exposures can be modified by changes in urban and transport planning. We emphasize the need for (1) the reduction of motorized traffic through the promotion of active and public transport and (2) the provision of green infrastructure, which are both suggested to provide PA opportunities and mitigation of air pollution, noise, and heat.

Full text, PDF, graphs, charts and 57 references

http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2016/6/EHP220.acco.pdf

“We estimated that annually almost 20% of mortality could be prevented if international recommendations for performance of physical activity, exposure to air pollution, noise, heat, and access to green space were complied with.”

“Cogently, children attending schools with higher levels of elemental carbon, nitrogen dioxide, and ultrafine particles both indoors and outdoors experienced substantially smaller growth in all the cognitive measurements; for example, a change from the first to the fourth quartile in indoor elemental carbon reduced the gain in working memory by 13.0%.”

Abstract

BACKGROUND

Air pollution is a suspected developmental neurotoxicant. Many schools are located in close proximity to busy roads, and traffic air pollution peaks when children are at school. We aimed to assess whether exposure of children in primary school to traffic-related air pollutants is associated with impaired cognitive development.

METHODS AND FINDINGS

We conducted a prospective study of children (n = 2,715, aged 7 to 10 y) from 39 schools in Barcelona (Catalonia, Spain) exposed to high and low traffic-related air pollution, paired by school socioeconomic index; children were tested four times (i.e., to assess the 12-mo developmental trajectories) via computerized tests (n = 10,112). Chronic traffic air pollution (elemental carbon [EC], nitrogen dioxide [NO2], and ultrafine particle number [UFP; 10-700 nm]) was measured twice during 1-wk campaigns both in the courtyard (outdoor) and inside the classroom (indoor) simultaneously in each school pair. Cognitive development was assessed with the n-back and the attentional network tests, in particular, working memory (two-back detectability), superior working memory (three-back detectability), and inattentiveness (hit reaction time standard error). Linear mixed effects models were adjusted for age, sex, maternal education, socioeconomic status, and air pollution exposure at home. Children from highly polluted schools had a smaller growth in cognitive development than children from the paired lowly polluted schools, both in crude and adjusted models (e.g., 7.4% [95% CI 5.6%-8.8%] versus 11.5% [95% CI 8.9%-12.5%] improvement in working memory, p = 0.0024). Cogently, children attending schools with higher levels of EC, NO2, and UFP both indoors and outdoors experienced substantially smaller growth in all the cognitive measurements; for example, a change from the first to the fourth quartile in indoor EC reduced the gain in working memory by 13.0% (95% CI 4.2%-23.1%). Residual confounding for social class could not be discarded completely; however, the associations remained in stratified analyses (e.g., for type of school or high-/low-polluted area) and after additional adjustments (e.g., for commuting, educational quality, or smoking at home), contradicting a potential residual confounding explanation.

CONCLUSIONS

Children attending schools with higher traffic-related air pollution had a smaller improvement in cognitive development.

Full text, aerial mapping, graphs, charts and 42 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4348510/

PLoS Medicine • March 2015

Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study

Author information

Sunyer J1, Esnaola M2, Alvarez-Pedrerol M2, Forns J2, Rivas I3, López-Vicente M2, Suades-González E4, Foraster M2, Garcia-Esteban R2, Basagaña X2, Viana M5, Cirach M2, Moreno T5, Alastuey A5, Sebastian-Galles N6, Nieuwenhuijsen M2, Querol X5.

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Reviews In Toxicology • December 2014

Cytotoxic evaluation of a mixture of eight pollutants at environmental relevant concentration

Author Information

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Abstract

“The ubiquitous presence of pollutants and the accurate evaluation of their potential risks for environmental and human health is an area of major concern. We have simulated an in vitro scenario of long-term exposure to a mixture of eight pollutants at real environmental concentrations using mammalian Vero cells. Our results demonstrate that cellular proliferation rates were significantly altered, either by inhibition or stimulation, depending on the mixture composition and the exposure time. We encourage the urgency of reviewing safety levels for emerging contaminants accepted by regulatory agencies, considering that mixtures of pollutants [synergy] represent a threat for environmental and human health.”

http://www.redalyc.org/articulo.oa?id=91932969009

CHAPTER THIRTY-FOUR

Xylitol

The Peer Review

Xylitol is categorized as a polyalcohol or sugar alcohol (alditol). Unlike other natural or synthetic sweeteners, xylitol is actively beneficial for dental health by reducing caries (cavities) to a third in regular use and helpful to remineralization. Multiple studies utilizing electron microscopy have indicated that xylitol is effective in inducing remineralization of deeper layers of demineralized enamel. Fair evidence was found that xylitol (as chewing gum, lozenges, nasal spray, etc.) reduced the incidence of acute middle ear infection in healthy children.

Xylitol is naturally found in low concentrations in the fibers of many fruits and vegetables, and can be extracted from various berries, oats, and mushrooms, as well as fibrous material such as corn husks and sugar cane bagasse. However, industrial production starts from xylan (a hemicellulose) extracted from hardwoods or corncobs, which is hydrolyzed into xylose and catalytically hydrogenated into xylitol. A study in rats found that xylitol had reduced or a lower caloric value and cariogenicity than sucrose. Please remember, there's a difference between industrially produced Xylitol and naturally occurring Xylitol.

PROPERTIES

One gram of xylitol contains 2.4 kilocalories (kcal), as compared to one gram of sugar, which has 3.87 kcal. Xylitol has virtually no aftertaste, and is advertised as "safe for diabetics and individuals with hyperglycemia." This tolerance is attributed to the lower effect of xylitol on a person's blood sugar, compared to that of regular sugars as it has an extremely low glycemic index of 7 (glucose has a GI of 100).

Xylitol also inhibits the growth of Streptococcus pneumoniae, as well as the attachment of Haemophilus influenzae on the nasopharyngeal cells. The perception of sweetness obtained from consuming xylitol causes the secretion of saliva which acts as a buffer against the acidic environment created by the microorganisms in dental plaque. Increase in salivation can raise the falling pH to a neutral range within a few minutes of xylitol consumption. However, despite these promising conjectures two systematic reviews of clinical trials could not find conclusive evidence that xylitol was indeed superior to other polyols such as sorbitol or equal to that of topical fluoride in its anti-caries effect.

In March, 2015, Cochrane published a review of the entire body of evidence surrounding xylitol's effects on dental caries. Their conclusion was that, while low-quality evidence suggests that over 2.5 to 3 years of use, a fluoride toothpaste containing xylitol may reduce caries when compared to a fluoride-only toothpaste, the remaining body of evidence is of low to very low quality and is insufficient to determine whether any other xylitol-containing products can prevent caries in infants, older children, or adults. Xylitol is categorized by the U.S. Food and Drug Administration as a food additive. Like other sugar alcohol-sweetened products, xylitol-sweetened products are allowed to be labeled with the claim that they do not promote dental cavities.

DIABETES

Possessing approximately 33% fewer calories, xylitol is a lower-calorie alternative to table sugar. Absorbed more slowly than sugar, it does not contribute to high blood sugar levels or the resulting hyperglycemia caused by insufficient insulin response. This characteristic has also

proven beneficial for people suffering from metabolic syndrome, a common disorder that includes insulin resistance, hypertension, hypercholesterolemia, and an Increased risk for blood clots. Xylitol is used as a sweetener in medicines, chewing gum and pastilles.

Xylitol chewing gum appears to decrease rates of acute otitis media in children going to daycare by 25%. Xylitol nasal sprays have also been shown to decrease incidence of acute otitis media as well as being a very effective way of both assisting and stimulating the body's own natural nasopharyngeal washing, and reducing both bacterial colonization and allergenic pollution, with their accompanying problems.

SAFETY

Xylitol has no known toxicity in humans. In one study, the participants consumed a diet containing a monthly average of 1.5 kg of xylitol with a maximum daily intake of 430 g with no apparent ill effects. Like most sugar alcohols, it has a laxative effect because sugar alcohols are not fully broken down during digestion. The effect depends upon the individual. In one study of 13 children, four experienced diarrhea when consuming over 65 grams per day.

As with other sugar alcohols, with the exception of erythritol, consumption in excess of one's laxation threshold (the amount of sweetener that can be consumed before abdominal discomfort sets in) can result in temporary gastrointestinal side effects, such as bloating, flatulence, and diarrhea. Adaptation, an increase of the laxation threshold, occurs with regular intake. Xylitol has a lower laxation threshold than some sugar alcohols, but is more easily tolerated than mannitol and sorbitol. Those of you that prefer enjoying your food rather than tolerating it may want to avoid Xylitol.

XYLITOL TOXICITY

Xylitol is fatal to dogs. According to the ASPCA Animal Poison Control Center, the number of cases of xylitol toxicosis in dogs has significantly increased since the first reports in 2002. Dogs that have ingested foods containing xylitol (greater than 100 milligrams of xylitol consumed per kilogram of bodyweight) have presented with low blood sugar (hypoglycemia), which can be life-threatening. Low blood sugar can result in a loss of coordination, depression, collapse and seizures in as little as 30 minutes. Intake of doses of xylitol (greater than 500 – 1000 mg/kg bwt) has been implicated in liver failure in dogs, which can be fatal. Possible cause of hypoglycemia experienced by dogs is the fact that the xylitol in gum is released more slowly and absorbed over longer period than when it is consumed as a pure form.

Nevertheless, in spite of its potential health benefits, Xylitol can also be dangerous to the human species. It retards bone absorption, can be synergistically toxic to cells, prevents weight gain and reduces food intake and more. You'll read about Xylitols potential beneficial health effects and its potential for harm in this chapter and decide for yourself.

“These results suggest that organ-specific responses to oxidative stress by these potential prooxidant compounds [Xylitol] may implicate a mechanism of their toxicities.”

Toxicology Letters • January 2016

Oxidative stress response in canine in vitro liver, kidney and intestinal models with seven potential dietary ingredients

Author information

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Abstract

In vitro cell culture systems are a useful tool to rapidly assess the potential safety or toxicity of chemical constituents of food. Here, we investigated oxidative stress and organ-specific antioxidant responses by 7 potential dietary ingredients using canine in vitro culture of hepatocytes, proximal tubule cells (CPTC), bone marrow-derived mesenchymal stem cells (BMSC) and enterocyte-like cells (ELC). Cellular production of free radical species by denatonium benzoate (DB), epigallocatechin gallate (EPI), eucalyptol (EUC), green tea catechin extract (GTE) and sodium copper chlorophyllin (SCC), tetrahydroisohumulone (TRA) as well as xylitol (XYL) were continuously measured for reactive oxygen/nitrogen species (ROS/RNS) and superoxide (SO) for up to 24h. DB and TRA showed strong prooxidant activities in hepatocytes and to a lesser degree in ELC. DB was a weak prooxidant in BMSC. In contrast DB and TRA were antioxidants in CPTC. EPI was prooxidant in hepatocytes and BMSC but showed prooxidant and antioxidant activity in CPTC. SCC in hepatocytes (12.5mg/mL) and CPTC (0.78mg/mL) showed strong prooxidant and antioxidant activity in a concentration-dependent manner. GTE was effective antioxidant only in ELC. EUC and XYL did not induce ROS/RNS in all 4 cell types. SO production by EPI and TRA increased in hepatocytes but decreased by SCC in hepatocytes and ELC. These results suggest that organ-specific responses to oxidative stress by these potential prooxidant compounds may implicate a mechanism of their toxicities.

http://www.ncbi.nlm.nih.gov/pubmed/26602166

“These results suggest that in vitro assays such as this may be useful for hazard assessment of food ingredients for altered hepatic function.”

Food And Chemical Toxicology • April 2015

Safety assessment of potential food ingredients in canine hepatocytes

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Abstract

This research aimed to develop in vitro methods to assess hazard of canine food ingredients. Canine hepatocytes were harvested and cell viability of clove-leaf oil (CLO), eugenol (EUG), lemongrass oil (LGO), guanosine monophosphate (GMP), inosine monophosphate (IMP), sorbose, ginger-root extract (GRE), cinnamon-bark oil (CBO), cinnamaldehyde (CINA), thymol oil (TO), thymol (THYM), and citric acid were assessed with positive controls: acetaminophen (APAP), aflatoxin B1 and xylitol. Molecular Toxicology PathwayFinder array (MTPF) analyzed toxicity mechanisms for LGO. LC50 for APAP was similar among human (3.45), rat (2.35), dog (4.26 mg/ml). Aflatoxin B1 had an LC50 of 4.43 (human), 5.78 (rat) and 6.05 (dog) µg/ml; xylitol did not decrease viability. LC50 of CLO (0.185 ± 0.075(SD)), EUG (0.165 ± 0.112), LGO (0.220 ± 0.012), GRE (1.54 ± 0.31) mg/ml; GMP (166.03 ± 41.83), GMP + IMP (208.67 ± 15.27) mM; CBO (0.08 ± 0.03), CINA (0.11 ± 0.01), TO (0.21 ± 0.03), THYM (0.05 ± 0.01), citric acid (1.58 ± 0.08) mg/ml, while sorbose was non-toxic. LGO induced up-regulation of 16 and down-regulation of 24 genes, which CYP and heat shock most affected. These results suggest that in vitro assays such as this may be useful for hazard assessment of food ingredients for altered hepatic function.

http://www.ncbi.nlm.nih.gov/pubmed/25660481

“These results indicate that xylitol has potential in therapy against lung cancer by inhibiting cell proliferation and inducing autophagy of A549 cells.”

Biotechnology Letters • May 2015

Xylitol induces cell death in lung cancer A549 cells by autophagy

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Abstract

Xylitol is a widely used anti-caries agent that has anti-inflammatory effects. We have evaluated the potential of xylitol in cancer treatment. It’s effects on cell proliferation and cytotoxicity were measured by MTT assay and LDH assay. Cell morphology and autophagy were examined by immunostaining and immunoblotting. Xylitol inhibited cell proliferation in a dose-dependent manner in these cancer cells: A549, Caki, NCI-H23, HCT-15, HL-60, K562, and SK MEL-2. The IC50 of xylitol in human gingival fibroblast cells was higher than in cancer cells, indicating that it is more specific for cancer cells. Moreover, xylitol induced autophagy in A549 cells that was inhibited by 3-methyladenine, an autophagy inhibitor. These results indicate that xylitol has potential in therapy against lung cancer by inhibiting cell proliferation and inducing autophagy of A549 cells.

http://www.ncbi.nlm.nih.gov/pubmed/25650339

“Dogs have been reported to experience lethal liver injury after accidental ingestion of xylitol. Because liver injury may be a serious consequence of canine immune-mediated reactions, antibodies produced against xylitol may attack the liver.”

Veterinary Immunology And Immunopathology • September 2012

Binding affinity of anti-xylitol antibodies to canine hepatic vessels

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Abstract

Xylitol is used as a sugar substitute in food products. Dogs have been reported to experience lethal liver injury after accidental ingestion of xylitol. Because liver injury may be a serious consequence of canine immune-mediated reactions, antibodies produced against xylitol may attack the liver. Therefore, in the present study, we evaluated whether binding sites for xylitol antibodies are located at the liver or not. Anti-xylitol antibodies were generated by immunization of rabbits with a xylose-bovine serum albumin conjugate. Immunohistological examination showed that binding sites for the anti-xylitol antibodies were located in the hepatic arteries and the portal veins. Western blotting analyses by using a canine liver homogenate showed 4 protein bands with different molecular weights which reacted with anti-xylitol antibodies. Therefore, binding of anti-xylitol antibodies to the vessels may be the first step in an immune-mediated pathogenic response in xylitol toxicity. Further studies are necessary to determine the effects of anti-xylitol antibodies on the liver in the pathogenesis of xylitol toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/22688382

Compendium • February 2010

Xylitol toxicity in dogs

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Abstract

"Xylitol, a sugar substitute used in sugar-free gum, oral care products, and baked goods, is gaining popularity in the United States. Xylitol consumption is considered harmless to people but is known to cause life-threatening toxicoses in dogs. Dogs that ingest doses of >0.1 g/kg of xylitol are at risk for developing hypoglycemia, while dogs that ingest >0.5 g/kg may develop acute liver failure. Treatment includes dextrose supplementation for hypoglycemia and aggressive monitoring, treatment, and supportive care for dogs experiencing hepatotoxicosis. The prognosis for dogs with uncomplicated hypoglycemia is good, whereas the prognosis for dogs that develop severe hepatotoxicosis is guarded to poor."

http://www.ncbi.nlm.nih.gov/pubmed/20473849

“The potential ability of various physical or chemical agents to enhance their effect when they are applied simultaneously with each other is well-known. The model suggests that the **synergism** is caused by the additional **effective damage arising from an interaction of sublesions induced by each agent.**”

Chemosphere • June 2008

Mathematical description, optimization and prediction of synergistic interaction of fluoride and xylitol

Author information

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Abstract

The potential ability of various physical or chemical agents to enhance their effect when they are applied simultaneously with each other is well-known. The purpose of this study was to adjust a simple mathematical model to describe, optimize and predict a synergistic interaction between fluoride and xylitol on acid production by mutans streptococci. The model suggests that the synergism is caused by the additional effective damage arising from an interaction of sublesions induced by each agent. These sublesions are considered to be ineffective when each agent is used individually. The predictions of the model were verified by comparison with experimental data published by other researchers. It was shown that the model describes the experimental data, predicts the greatest value of the synergistic effect and the condition under which it can be achieved. The synergistic effect appeared to decline with any deviation from the optimal value of the ratio of effective damages produced by each agent alone.

http://www.ncbi.nlm.nih.gov/pubmed/18367232

Applied Biochemistry And Biotechnology • Spring 2005

Effects of aliphatic acids, furfural, and phenolic compounds on Debaryomyces hansenii CCMI 941

Author information

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Abstract

“Debaryomyces hansenii is a polyol overproducing yeast that can have a potential use for upgrading lignocellulosic hydrolysates. Therefore, the establishment of its tolerance to metabolic inhibitors found in hydrolysates is of major interest. We studied the effects of selected aliphatic acids, phenolic compounds, and furfural. Acetic acid favored biomass production for concentrations <6.0 g/L. Formic acid was more toxic than acetic acid and **induced xylitol accumulation** (maximum yield of 0.21 g/g of xylose). All tested phenolics strongly decreased the specific growth rate. Increased toxicity was found for hydroquinone, syringaldehyde, and 4-methylcatechol and was correlated to the compound’s hydrophobicity. Increasing the amount of furfural led to longer lag phases and had a detrimental effect on specific growth rate and biomass productivity.”

http://www.ncbi.nlm.nih.gov/pubmed/15917618

“Mannose and xylitol butyric derivatives would appear to have exciting potential in treatment of beta-Hemoglobinopathies, sickle cell anemia and cancer.”

European Journal Of Pharmaceutical Sciences • January 1999

Regioselective synthesis and biological profiling of butyric and phenylalkylcarboxylic esters derivated from D-mannose and xylitol: influence of alkyl chain length on acute toxicity

Author information

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Abstract

Regiospecific synthesis of 12 novel n-butyric and phenylalkylcarboxylic monoesters of mannose and xylitol was achieved. The strategy adopted, avoided a tedious intramolecular transesterification step, previously described for the synthesis of analogous compounds and permitted the facile synthesis of a new generation of stable derivatives. The general tolerance of the drugs has been assayed after intravenous administration of a bolus dose into mice. Monobutyric esters showed a low toxicity commensurate with the requirements for future development. A relationship was observed between chain length and toxicity. In contrast, phenylacetic, 3-phenylpropionic and 4-phenylbutyric esters were found to be toxic. Phenylbutyric esters induced marked and specific neuromuscular damage. Preliminary biological investigations of the new series of monobutyric esters showed them to retain the benificial biological properties of butyric acid whilst remaining relatively non toxic. They induced an inhibition of in vitro proliferation of 10 human cases of de novo acute myeloid leukemia (AML) primary cultures and AML established cell lines. AML blasts growth appeared to be blocked and cell differentiation was established. Transcription and expression of maturation markers and finally apoptosis were observed. Moreover, human gamma-chain hemoglobin (HbF) synthesis in erythroleukemia cells was stimulated by monobutyric esters. Mannose and xylitol butyric derivatives would appear to have exciting potential in treatment of beta-Hemoglobinopathies, sickle cell anemia and cancer.

http://www.ncbi.nlm.nih.gov/pubmed/9845786

“Feeding the xylitol diet partially, but significantly, prevented the reductions in body weight gain and food intake ...”

British Poultry Science • September 1999

Effect of dietary xylitol on growth and inflammatory responses in immune stimulated chickens

Author information

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Abstract

It has been argued that stimulation of the immune system depresses performance. Accordingly, an experiment was conducted to determine the effect of dietary xylitol (150 g/kg diet) on growth and selected inflammatory responses in male broiler chickens. During the final 6 d of the experimental periods, chicks were injected with antigens: Escherichia coli lipopolysaccharide (LPS) on days 1, 3 and 5 and with Sephadex-G50 superfine on days 2 and 4 to stimulate macrophage functions. The immune stimulation reduced body weight gain and food intake, but enhanced alpha 1 acid glycoprotein (AGP) concentration and interleukin (IL-1) like activity in plasma. Feeding the xylitol diet partially, but significantly, prevented the reductions in body weight gain and food intake, without affecting the early stage of inflammatory responses triggered by LPS and Sephadex injections.

http://www.ncbi.nlm.nih.gov/pubmed/10579417

“In conclusion, dietary xylitol, sorbitol and to a lesser degree D-mannitol supplementations in rats retard bone resorption, whereas dietary erythritol has no effect.”

The Journal Of Nutrition • July 1996

Dietary xylitol, sorbitol and D-mannitol but not erythritol retard bone resorption in rats

Author information

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Abstract

The aim of the present study was to compare the ability of four dietary polyols to reduce bone resorption. Urinary excretion of 3H radioactivity from [3H]tetracycline-prelabeled rats was used as a marker of bone resorption. After prelabeling, the rats were divided randomly into five groups of 10, and fed for 1 mo a nonpurified diet that was supplemented in four groups with either xylitol, sorbitol, D-mannitol or erythritol, respectively, to give a polyol concentration of 1 mol/kg. Xylitol (42%), sorbitol (44%) and to a lesser degree D-mannitol (23%) decreased the excretion of 3H relative to the basal diet. The erythritol group, however, did not differ from the controls. Sorbitol caused continuous diarrhea, whereas in the other groups, intestinal adaptation took place during the 1st wk of polyol feeding. In conclusion, dietary xylitol, sorbitol and to a lesser degree D-mannitol supplementations in rats retard bone resorption, whereas dietary erythritol has no effect.

http://www.ncbi.nlm.nih.gov/pubmed/8683349

Toxicological Applied Pharmacology • September 1996

Vitamin D3, lactose, and xylitol stimulate chromaffin cell proliferation in the rat adrenal medulla

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Abstract

Chronic consumption by rats of diets rich in sugars or sugar alcohols leads to an increased incidence of pheochromocytomas. This relationship is hypothesized to be based on altered Ca2+ homeostasis due to increased intestinal Ca2+ absorption. Other agents associated with pheochromocytomas in rats in long-term toxicity studies have been shown to increase chromaffin cell proliferation, leading to the suggestion that the tumors occur secondarily to increased chromaffin cell turnover. We have demonstrated marked stimulation of chromaffin cell proliferation by vitamin D3, a potent stimulus to Ca2+ absorption not previously associated with adrenal medullary toxicity. This effect is detectable during the first week of dietary supplementation and persists throughout a 4-week time course. Lactose and xylitol, representative of sugars and sugar alcohols associated with pheochromocytomas, are also mitogenic but to a lesser extent, with their effects first detectable during Week 4 of dietary supplementation. Vitamin D3, its active metabolite calcitriol, lactose, and xylitol all fail to stimulate proliferation of rat chromaffin cells in vitro. The mitogenic effects of these agents may be mediated presynaptically in vivo. The data suggest that altered Ca2+ homeostasis may increase chromaffin cell proliferation and support the hypothesis that diets containing high concentrations of sugars and sugar alcohols cause pheochromocytomas in rats secondarily by this mechanism.

http://www.ncbi.nlm.nih.gov/pubmed/8806877

PHEOCHROMOCYTOMA

In simple language a pheochromocytoma is a rare, usually noncancerous (benign) tumor that develops in cells in the center of an adrenal gland. You have two adrenal glands, one above each kidney. Your adrenal glands produce hormones that give instructions to virtually every organ and tissue in your body. If you have a pheochromocytoma, an adrenal gland releases hormones that cause persistent or episodic high blood pressure. If left untreated, a pheochromocytoma can result in severe or life-threatening damage to other body systems, especially the cardiovascular system. Most people with a pheochromocytoma are

> “Chronic consumption by rats of diets rich in sugars or sugar alcohols leads to an increased incidence of pheochromocytomas.”

between the ages of 20 and 50, but the tumor can develop at any age. Surgical treatment to remove a pheochromocytoma usually returns blood pressure to normal. In more complex terms pheochromocytoma or phaeochromocytoma (PCC) is a neuroendocrine tumor of the medulla of the adrenal glands (originating in the chromaffin cells), or extra-adrenal chromaffin tissue that failed to involute after birth, that secretes high amounts of catecholamines, mostly norepinephrine, plus epinephrine to a lesser extent. Extra-adrenal paragangliomas (often described as extra-adrenal pheochromocytomas) are closely related, though less common, tumors that originate in the ganglia of the sympathetic nervous system and are named based upon the primary anatomical site of origin. The signs and symptoms of a pheochromocytoma are those of sympathetic nervous system hyperactivity, including:

- Skin sensations
- Flank pain
- Elevated heart rate
- Elevated blood pressure, including paroxysmal (sporadic, episodic) high blood pressure, which sometimes can be more difficult to detect. Another clue to the presence of pheochromocytoma is orthostatic hypotension (a fall in systolic blood pressure greater than 20 mmHg or a fall in diastolic blood pressure greater than 10 mmHg upon standing);
- Palpitations
- Anxiety often resembling that of a panic attack
- Diaphoresis (excessive sweating)
- Headaches – most common symptom
- Pallor
- Weight loss
- Localized amyloid deposits found microscopically
- Elevated blood glucose level (due primarily to catecholamine stimulation of lipolysis (breakdown of stored fat) leading to high levels of free fatty acids and the subsequent in-

hibition of glucose uptake by muscle cells. Further, stimulation of beta-adrenergic receptors leads to glycogenolysis and gluconeogenesis and thus elevation of blood glucose levels).

A pheochromocytoma can also cause resistant arterial hypertension. A pheochromocytoma can be fatal if it causes a hypertensive emergency, that is, severely high blood pressure that impairs one or more organ systems (formerly called "malignant hypertension"). This hypertension is not well controlled with standard blood pressure medications.

Not all patients experience all of the signs and symptoms listed. The most common presentation is headache, excessive sweating, and increased heart rate, with the attack subsiding in less than one hour. Tumors may grow large, but most are smaller than 10 centimetres (4 in).

TUMOR SIZE AND LOCATION

Although pheochromocytomas may grow to large size (>3 kg), most weigh <100 g and are <10 cm in diameter. Pheochromocytomas are highly vascular. Most are located within the abdomen in association with the celiac, superior mesenteric, and inferior mesenteric ganglia and the organ of Zuckerkandl. Approximately 10% are in the thorax, 1% are within the urinary bladder, and less than 3% are in the neck, usually in association with the sympathetic ganglia or the extracranial branches of the ninth cranial nerves.

The massive release of catecholamines in pheochromocytoma can cause damage to heart cells. This damage may be due to either compromising the coronary microcirculation or by direct toxic effects on the heart cells.

EPIDEMIOLOGY

Pheochromocytoma is seen in between 2–8 in 1,000,000, with approximately 1000 cases diagnosed in United States yearly. It mostly occurs in young or middle age adults, though presents earlier in hereditary cases and it is also called 10% tumor .

- About 10% of adrenal cases are bilateral (suggesting hereditary disease)
- About 10% of adrenal cases occur in children (also suggesting hereditary disease)
- About 15% are extra-adrenal (located in any orthosympathetic tissue): Of these 9% are in the abdomen, and 1% are located elsewhere. Some extra-adrenal pheochromocytomas are probably actually paragangliomas, but the distinction can only be drawn after surgical resection.
- About 11.1% of adrenal cases are malignant, but this rises to 30% for extra-adrenal cases
- About 15-20% are hereditary[15]
- About 5% are caused by VHL disease
- About 3% recur after being resected
- About 14% of affected individuals do not have arterial hypertension (Campbell's Urology)

“Although xylitol decreased food intake and also delayed gastric emptying, these effects may be unrelated. Our data suggest a role for xylitol as a potentially important agent in dietary control.”

American Journal Of Clinical Nutrition • April 1987

Effects of xylitol on gastric emptying and food intake

Shafer RB, Levine AS, Marlette JM, Morley JE.

Abstract

We studied the effects of xylitol, the pentose-sugar alcohol, on gastric emptying of the solid-food component of a complex meal. Gastric emptying was measured in human volunteers by utilizing a standardized radiolabeled scrambled-egg meal. After ingestion of 25 g xylitol, gastric emptying was markedly prolonged (T-1/2 58 +/- 5 min control vs 91 +/- 7 min after xylitol [p less than 0.01]). Since delayed gastric emptying may affect food intake, we evaluated the effects of xylitol on calorie intake. Food intake after oral preloading with water resulted in intake of 920 +/- 60 kcal vs 690 +/- 45 kcal after 25 g of xylitol. In contrast, a preload of glucose, fructose, or sucrose failed to suppress food intake. Although xylitol decreased food intake and also delayed gastric emptying, these effects may be unrelated. Our data suggest a role for xylitol as a potentially important agent in dietary control.

http://www.ncbi.nlm.nih.gov/pubmed/3565302

“The increases in the levels of urinary organic acids in the polyol-fed rats were explained in terms of impaired mitochondrial oxidation of these acids and of impaired conversion of methylmalonic acid to succinic acid.”

Toxicology And Applied Pharmacology • September 1987

Organic aciduria in rats fed high amounts of xylitol or sorbitol

By M. M. Hämäläinen

Abstract

The acidification of urine during polyol feeding was investigated with 27 Long-Evans male rats (aged 12 weeks) which were fed a xylitol diet (X), a sorbitol diet (S), or a basal diet for 4 weeks. The amount of polyols in the diet was increased from 5% to the final 20% level within 3 weeks. The polyol-fed animals showed reduced weight gain, lowered urine pH (from 6.5 to 5.6), and a 4-fold increase in the titratable acid excretion. X and S increased the daily urine volumes by 49 and 63%, respectively, but did not affect the wet weight or the pH values of the feces. as chromatographic-mass spectrometric analyses of organic acids revealed highly increased amounts of methylmalonic acid (13- to 20-fold) and 2-oxoglutaric acid (4- to 5-fold) in the urine of polyol-fed rats. The urinary excretion of citric acid and malic acid was also increased significantly (2- to 4-fold). The acidity of urine was not reflected in the blood acid-base balance of the animals. The increases in the levels of urinary organic acids in the polyol-fed rats were explained in terms of impaired mitochondrial oxidation of these acids and of impaired conversion of methylmalonic acid to succinic acid.

http://www.ncbi.nlm.nih.gov/pubmed/3629597

“Although all three polyols [galactitol, mannitol or xylitol] retarded the growth rate of the animals, the polyols were well tolerated.”

The Journal Of Nutrition • July 1985

Metabolic effects in rats of high oral doses of galactitol, mannitol and xylitol

By KK Mäkinen and MM Hämäläinen

Abstract

The effect of feeding high amounts of polyols on rat metabolism was studied. Adult male rats were fed the basal diet or the same diet to which had been added either galactitol, mannitol or xylitol for 8 wk (final polyol level 200 g/kg diet). Although all three polyols retarded the growth rate of the animals, the polyols were well tolerated. The four experimental groups did not differ significantly (P greater than 0.01) in the following analyses: blood lactic acid and serum transaminases, amylase, lactate dehydrogenase, triglycerides, insulin, glucagon and corticosterone. Compared to rats fed the basal diet, galactitol rats had higher blood hemoglobin levels (P less than 0.01); those fed galactitol or mannitol had lower blood glucose (P less than 0.001 and P less than 0.01, respectively), and those fed mannitol had higher blood pyruvic acid (P less than 0.01). Rats fed any of the polyols had lower serum total cholesterol and liver ascorbic acid (P less than 0.001) than control rats. Rats fed mannitol had higher liver glycogen levels (P less than 0.001) than control rats. Irrespective of the structural differences between the pentitol and the hexitols, a number of common metabolic effects were found. The proposed mechanisms of these effects include 1) the slow absorption and the rapid intraluminal metabolism of the polyols and 2) the similar handling of these polyols in the liver by a dehydrogenase.

http://www.ncbi.nlm.nih.gov/pubmed/3925094

CHAPTER THIRTY-FIVE

Pharmaceuticals And Personal Care Products - PPCPs
• As Tap Water, Surface Water (oceans, rivers and streams) & Waste Water Pollutants •

The Peer Review

It just makes sense to want clean, safe water. The thought of drinking polluted water or bathing in a murky mess is very distasteful. Because our desire to have safe water sources is so strong, we have developed increasingly sophisticated methods for monitoring and detecting pollutants in the water. Having these improved tests means that groundwater and surface water contamination can be detected at lower and lower levels—even down to nanograms per liter. And that has led to an emerging public awareness about pollutants. Pharmaceuticals and personal care products (PPCPs) are some of these emerging contaminants being found in tap water.

Lately new information about PPCPs turning up in the environment has been making headlines and raising questions about potential human health risks. And all of this attention has led scientists to realize that they don't know much about the kinds of impacts PPCPs may have. According to the U.S. Environmental Protection Agency (EPA), two classes of PPCPs are considered therapeutics: antibiotics and steroidal hormones. Antibiotics may cause resistance among pathogens, making some bugs difficult to kill. Steroidal hormones overlap with another class known as endocrine disruptors. Not much is known about any other class of PPCPs. And PPCP levels are not regulated in drinking water.

Researchers have detected PPCPs in quantifiable amounts in samples collected from U.S. waterways. PPCPs that have been found include medications for pain, depression, and colds; birth control pills; caffeine; hair products; cleaning supplies and pesticides.

Some of these products contain endocrine disrupting compounds and other contaminants that researchers fear may harm aquatic life. However, research has only just begun and little evidence exists about the consequences on human or aquatic life.

Significant sources of PPCPs include pharmaceutical and chemical manufacturing facilities, hospitals, nursing homes, long-term care facilities, pharmacies, veterinary operations, landfill leachate, septage tank haulers, meat processors, and runoff from animal feeding operations where large quantities of antibiotics and other drugs are used.

Surprisingly, however, one of the largest sources of PPCPs is the typical household where PPCPs enter wastewater treatment plants through human excrement, flushing unused medications, and washing chemicals down the drain. And as we use more and better deodorants, disinfectants, birth control products, and pesticides, the amount of PPCPs found in the environment will become greater. No one knows what, if anything, PPCPs may be doing to septic system performance or water treatment plant performance let alone the total environment itself—humans, animals, plants and insects.

While there is no certainty, anti-bacterial soaps and cleansers may have an effect on the bacteriological requirements of the treatment system. Without the proper balance of bacteria in the system, waste may not break down as it should, and the result could be early septic or wastewater treatment system failure.

What are the possible health effects?

There are more questions about the possible health effects of PPCPs on humans and aquatic life than there are answers. Most of the research to date has only proven that various PPCPs are present in the environment.

Because such a broad mix of compounds have been found, the U.S. Geological Survey thinks it is impossible to predict what any possible health effects might be. Researchers will have to take this complex mixture into account before they can say that this compound or these sets of compounds are causing an observed effect.

Most of the research on the effects of PPCPs involves antibiotic and hormone drugs. Research has shown that sex steroids from oral contraceptives and other similar chemicals can feminize male fish and change behaviors of either sex. A three-year study by a research team at Brunel University in the United Kingdom found that many final sewage effluents contain estrogenic hormones believed to originate from women's urine. The research began after the discovery that male fish in the lagoons of a United Kingdom waste-water treatment plant had become partly feminized. In Europe, researchers have tied a decline in human male sperm count to low levels of birth control hormones in the environment.

Antibiotics are viewed as "wonder drugs" with their ability to treat infectious bacterial diseases that were often killers. However, widespread use of antibiotics by both humans and in livestock has led to antibiotic resistant bacteria. Traces of antibiotics in watersheds may only magnify this problem.

Studies within the U.S. indicate that groundwater that is down gradient from hospital and veterinary clinic waste may contain varying amounts of antibiotics, i.e. sulfonamides and trimethoprim. One Wisconsin study found antibiotics in wastewater effluent as well as adjacent groundwater monitoring wells. According to this study, however, samples contained only minute amounts of antibiotics (<10 micrograms per liter [ug/L]), and the size of the treatment facility had no effect on whether antibiotics were found.

What are endocrine disruptors?

Some chemicals, both natural and man-made, can interfere with the hormonal systems of humans, animals, and aquatic life. Endocrine disrupting chemicals (EDCs) can act in a number of ways in different parts of the body. They may:

- reduce the production of hormones in endocrine glands
- Affect the release of hormones from endocrine glands
- copy or counteract the action of hormones at target tissues, or
- speed up the metabolism of hormones and so reduce their action

In many cases, it is not yet clear exactly how endocrine disrupting chemicals act, even in some cases where a link has been shown between endocrine disrupting chemical exposure and an adverse effect.

According to the National Institute of Environmental Health Sciences (NIEHS), endocrine disruptors may be responsible for emerging cases of breast and other cancers, as well as endometriosis and subfertility or infertility. Some suspected endocrine disruptors come from chlorinated organic chemicals, such as DDT, toxaphene, and kepone. They also come from herbicides, such as 2,4-D; mercury; styrene; dioxin; polychlorinated biphenols and bisphenol analogues.

Preventing PPCPs from Entering the Environment

One key to limiting the amount of PPCPs that enter the environment is direct disposal of unused drugs. But, because this country doesn't have a cohesive set of regulations or even guidance for proper disposal of unused drugs, a consistent guide needs to be created about the safest way to dispose of drugs.

Another aspect that could limit the introduction of PPCPs into the environment has to do with their intended use. Although not much can be done about chemicals that are considered human medicine, according to EPA, there are a wide number of things that can be done with respect to drug design and delivery that can actually lower doses of drugs or make drugs more environmentally friendly. Also, users can change their habits regarding antibacterial soaps, disinfectants, and other PPCPs used around the home.

PPCPs and Water Reuse

EPA researchers note that one of the largest reasons people have fears about PPCPs is they can come from excrement. The agency notes that also may be the reason that some water reuse projects fail, such as various toilet-to-tap programs, which propose to reclaim wastewater for drinking.

Water reuse is common in Hawaii since nearly all of the state's drinking water supply is obtained from unconfined groundwater aquifiers. Drinking water for the one million residents of Oahu Island in Hawaii is obtained from groundwater. In Oahu, treated wastewater is used to irrigate some agricultural lands and some of the 35 golf courses on the island. Therefore, protecting this groundwater from possible contamination is important.

Roger Babcock, Ph.D., associate professor of civil and environmental engineering at the University of Hawaii, is currently involved with a study on Hawaii's Oahu Island to screen groundwater, wastewater, and reclaimed water for PPCPs. In addition to PPCP detection, the study also determines soil sorption characteristics of selected pharmaceutical compounds and the fate and transport of PPCPs in recycled water during percolation through soil in field-test plots.

"*What we are trying to do is figure out what the fate of these compounds is when they are discharged into the environment*," Babcock said.

Currently, recycled water cannot be used over an aquifer and this was the catalyst for the study, Babcock said. "*Recycled water is generally only approved for use in areas where it's not over a drinking water supply, but there is a proposal for fairly large-scale reuse over a potable aquifer. This study is aimed at finding out if that's okay*," he said.

Results of the study so far indicate PPCPs were found in treated and untreated wastewater, but no PPCPs were detected in the groundwater samples taken.

Unanswered Questions

It will probably take many years to solve the mystery of PPCPs. Currently, more questions are generated than answers about the potential effects of PPCPs, but one thing is certain—detection of PPCPs does have an emotional impact on all levels of society.

Researchers have speculated that people have a far stronger reaction to the detection of PPCPs verses the detection of pesticides in the environment because ibuprofen and caffeine are drugs that the public uses. Now that we know these compounds are out there, the big question is—how much of an impact do PPCPs have on the environment and what do we do about it?

Original Essay in PDF format:

http://www.nesc.wvu.edu/pdf/WW/publications/pipline/pl_wi07.pdf

“This work analyses the presence of forty-eight emerging pollutants, including twenty-five drugs of abuse and metabolites, seventeen cytostatic drugs and six iodinated contrast media, in tap water from the Madrid Region.”

Environment International • January 2016

Drugs of abuse, cytostatic drugs and iodinated contrast media in tap water from the Madrid region (central Spain): A case study to analyse their occurrence and human health risk characterization

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Abstract

This work analyses the presence of forty-eight emerging pollutants, including twenty-five drugs of abuse and metabolites, seventeen cytostatic drugs and six iodinated contrast media, in tap water from the Madrid Region. Analysis of the target compounds in the tap water was performed by means of (on-line or off-line) solid-phase extraction followed by analysis by liquid chromatography-tandem mass spectrometry. A preliminary human health risk characterization was undertaken for each individual compound and for different groups of compounds with a common mechanism of action found in tap water. The results of the study showed the presence of eight out of the twenty-five drugs of abuse and metabolites analysed, namely, the cocainics cocaine and benzoylecgonine, the amphetamine-type stimulants ephedrine, 3,4-methylenedioxymethamphetamine and methamphetamine, the opioid methadone and its metabolite 2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine and, finally caffeine at concentrations ranging from 0.11 to 502 ng L(-1). Four out of the six analysed iodinated contrast media, namely, diatrizoate, iohexol, iomeprol and iopromide, were detected in at least one sample, with concentration values varying between 0.4 and 5 ng L(-1). Cytostatic compounds were not detected in any sample. Caffeine was the substance showing the highest concentrations, up to 502 ng L(-1), mainly in the drinking water sampling point located in Madrid city. Among the other drugs of abuse, the most abundant compounds were cocaine and benzoylecgonine, detected at concentrations ranging from 0.11 to 86 ng L(-1) and from 0.11 to 53 ng L(-1), respectively. Regarding iodinated contrast media, iohexol was the most ubiquitous and abundant compound, with a frequency of detection of 100% and concentrations from 0.5 to 5.0 ng L(-1) in basically the same range in all sampling points. Taking into account the results and types of treatment applied, ozonisation plus granular activated carbon filtration appears to be efficient in the removal of cocaine and benzoylecgonine. For the amphetamine-type stimulants, opioids and caffeine, ozonisation plus granular activated carbon filtration and ultrafiltration plus reverse osmosis showed higher removal efficiency than sand filtration. The human health risk characterization performed indicates that the lifetime consumption of the tap waters analysed has associated a negligible human health concern.

http://www.ncbi.nlm.nih.gov/pubmed/26571428

> “The results of this study suggest that Metformin and Guanylurea could be distributed over a large fraction of the world’s potable water sources and oceans. With no natural degradation processes, these compounds can be easily reintroduced to humans as they enter the food chain.”

Water Research • April 2016

Occurrence of the antidiabetic drug Metformin and its ultimate transformation product Guanylurea in several compartments of the aquatic cycle

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Abstract

In 2030, the World Health Organization estimates that more than 350 million people will be diagnosed with diabetes. Consequently, Metformin - the biguanide drug of choice orally administered for diabetes type II - is anticipated to see a spike in production. Unlike many pharmaceutical drugs, Metformin (Met) is not metabolized by humans but passes through the body unchanged. Entering aquatic compartments, such as in sewage, it can be bacterially transformed to the ultimate transformation product Guanylurea (Gua). Sampling over one week (n=5) from a Southern German sewage treatment plant revealed very high average (AV) concentrations in influent (AVMet=111,800ng/L, AVGua=1300ng/L) and effluent samples (AVMet=4800ng/L, AVGua=44,000ng/L). To provide a more complete picture of the distribution and potential persistence of these compounds in the German water cycle, a new, efficient and highly sensitive liquid chromatography mass spectrometric method with direct injection was used for the measurement of Metformin and Guanylurea in drinking, surface, sewage and seawater. Limits of quantification (LOQ) ranging from 2-10ng/L allowed the detection of Metformin and Guanylurea in different locations such as: Lake Constance (n=11: AVMet=102ng/L, AVGua=16ng/L), river Elbe (n=12: AVMet=472ng/L, AVGua=9ng/L), river Weser (n=6: AVMet=349ng/L, AVGua=137ng/L) and for the first time in marine North Sea water (n=14: AVMet=13ng/L, AVGua=11ng/L). Based on daily water discharges, Metformin loads of 15.2kg/d (Elbe) and 6.4kg/d (Weser) into the North Sea were calculated. Lake Constance is used to abstract potable water which is further purified to be used as drinking water. A first screening of two tap water samples contained 2ng/L and 61ng/L of Metformin, respectively. The results of this study suggest that Metformin and Guanylurea could be distributed over a large fraction of the world’s potable water sources and oceans. With no natural degradation processes, these compounds can be easily reintroduced to humans as they enter the food chain.

http://www.ncbi.nlm.nih.gov/pubmed/24954924

“These data provide evidence that human precursors can increase mutagenic potencies of pools and spas and that this increase is associated with increased Disinfection By-Products concentrations.”

Environmental Science And Technology • April 2016

Progressive Increase in Disinfection Byproducts and Mutagenicity from Source to Tap to Swimming Pool and Spa Water: Impact of Human Inputs

Daiber EJ, DeMarini DM, Ravuri SA, Liberatore HK,
Cuthbertson AA, Thompson-Klemish A, Byer JD, Schmid JE,
Afifi MZ, Blatchley ER, Richardson SD.

Abstract

Pools and spas are enjoyed throughout the world for exercise and relaxation. However, there are no previous studies on mutagenicity of disinfected spa (hot tub) waters or comprehensive identification of disinfection byproducts (DBPs) formed in spas. Using 28 water samples from 7 sites, we report the first integrated mutagenicity and comprehensive analytical chemistry of spas treated with chlorine, bromine, or ozone, along with pools treated with these same disinfectants. Gas chromatography with high-resolution mass spectrometry and membrane-introduction mass spectrometry were used to comprehensively identify and quantify DBPs and other contaminants. Mutagenicity was assessed by the Salmonella mutagenicity assay. More than 100 DBPs were identified, including a new class of DBPs, bromoimidazoles. Brominated pool/spa waters were 1.8X more mutagenic than chlorinated ones; spa waters were 1.7X more mutagenic than pools. Pool and spa samples were 2.4 and 4.1X more mutagenic, respectively, than corresponding tap waters. The concentration of the sum of 21 DBPs measured quantitatively increased from finished to tap to pool to spa; and mutagenic potency increased from finished/tap to pools to spas. Mutagenic potencies of samples from a chlorinated site correlated best with brominated haloacetic acid concentrations (Br-HAAs) ($r = 0.98$) and nitrogen-containing DBPs (N-DBPs) ($r = 0.97$) and the least with Br-trihalomethanes ($r = 0.29$) and Br-N-DBPs ($r = 0.04$). The mutagenic potencies of samples from a brominated site correlated best ($r = 0.82$) with the concentrations of the 9 HAAs, Br-HAAs, and Br-DBPs. Human use increased significantly the DBP concentrations and mutagenic potencies for most pools and spas. These data provide evidence that human precursors can increase mutagenic potencies of pools and spas and that this increase is associated with increased DBP concentrations.

http://www.ncbi.nlm.nih.gov/pubmed/27124361

Environmental Toxicology Chemistry • April 2016

Chemical and biochemical characterization and in vivo safety evaluation of pharmaceuticals in drinking water

Author information

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Abstract

The water constituents that are currently subject to legal control are only a small fraction of the vast number of chemical substances and microorganisms that may occur in both the environment and in water resources. The main objective of this work is to study the health impact resulting from exposure to a mixture of pharmaceuticals that have been detected in tap water at low doses. Analysis of atenolol, caffeine, erythromycin, carbamazepine and their metabolites in blood, urine, feces, fat tissue, liver and kidney after exposure to a mixture of these pharmaceuticals in treated drinking water were performed. The effects of this exposure were assessed in rats by measuring biochemical markers of organs injury or dysfunction. Simultaneously, the selected pharmaceuticals were also quantified in both physiological fluids and organ homogenates by liquid chromatography/tandem mass spectrometry (performed in multiple reaction monitoring mode and full scan mode). Following exposure of rats to a concentration of a pharmaceutical, which was ten times higher than the concentration known to be present in tap water, trace levels of some pharmaceuticals and their metabolites were detected in biological samples. This exposure did, however, not lead to significant organ injury/ dysfunction. Thus, we report here an experimental model that can be used to characterize the safety profile of pharmaceuticals in treated drinking water using a multiorgan toxicity approach.

http://www.ncbi.nlm.nih.gov/pubmed/27061931

Environmental Toxicology Chemistry • April 2016

Pharmaceuticals in the environment—Global occurrences and perspectives

Author information

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Abstract

Pharmaceuticals are known to occur widely in the environment of industrialized countries. In developing countries, more monitoring results have recently become available, but a concise picture of measured environmental concentrations (MECs) is still elusive. Through a comprehensive literature review of 1016 original publications and 150 review articles, the authors collected MECs for human and veterinary pharmaceutical substances reported worldwide in surface water, groundwater, tap/drinking water, manure, soil, and other environmental matrices in a comprehensive database. Due to the heterogeneity of the data sources, a simplified data quality assessment was conducted. The database reveals that pharmaceuticals or their transformation products have been detected in the environment of 71 countries covering all continents. These countries were then grouped into the 5 regions recognized by the United Nations (UN). In total, 631 different pharmaceutical substances were found at MECs above the detection limit of the respective analytical methods employed, revealing distinct regional patterns. Sixteen substances were detected in each of the 5 UN regions. For example, the anti-inflammatory drug diclofenac has been detected in environmental matrices in 50 countries, and concentrations found in several locations exceeded predicted no-effect concentrations. Urban wastewater seems to be the dominant emission pathway for pharmaceuticals globally, although emissions from industrial production, hospitals, agriculture, and aquaculture are important locally. The authors conclude that pharmaceuticals are a global challenge calling for multistakeholder approaches to prevent, reduce, and manage their entry into and presence in the environment, such as those being discussed under the Strategic Approach to International Chemicals Management, a UN Environment Program.

http://www.ncbi.nlm.nih.gov/pubmed/26666847

“Lead results from 78,971 water samples collected in four Canadian provinces from elementary schools, daycares, and other large buildings using regulatory and investigative sampling protocols were analyzed to provide lead concentration distributions. Maximum concentrations reached 13,200 and 3890 µg/L following long and short stagnation periods respectively. High lead levels were persistent in some large buildings, reflected by high median values considering all taps, or specific to a few taps in the building.”

Water Research • April 2016

Evaluation of exposure to lead from drinking water in large buildings

Author information

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Abstract

Lead results from 78,971 water samples collected in four Canadian provinces from elementary schools, daycares, and other large buildings using regulatory and investigative sampling protocols were analyzed to provide lead concentration distributions. Maximum concentrations reached 13,200 and 3890 µg/L following long and short stagnation periods respectively. High lead levels were persistent in some large buildings, reflected by high median values considering all taps, or specific to a few taps in the building. Simulations using the Integrated Uptake Biokinetic (IEUBK) model and lead concentrations after 30 min of stagnation in the dataset showed that, for most buildings, exposure to lead at the tap does not increase children’s blood lead levels (BLLs). However, buildings or taps with extreme concentrations represent a significant health risk to young children attending school or daycare, as the estimated BLL far exceeded the 5 µg/dL threshold. Ingestion of water from specific taps could lead to acute exposure. Finally, for a few taps, the total daily lead intake reached the former World Health Organization (WHO) tolerable level for adults, suggesting potential health risks.

http://www.ncbi.nlm.nih.gov/pubmed/27132198

“The water constituents that are currently subject to legal control are only a small fraction of the vast number of chemical substances and microorganisms that may occur in both the environment and in water resources [tap water].”

Environmental And Toxicological Chemistry • April 2016

Chemical and biochemical characterization and in vivo safety evaluation of pharmaceuticals in drinking water

Author information

Gaffney VJ1, Mota-Filipe H1,2, Pinto RA1,3,
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Abstract

The water constituents that are currently subject to legal control are only a small fraction of the vast number of chemical substances and microorganisms that may occur in both the environment and in water resources. The main objective of this work is to study the health impact resulting from exposure to a mixture of pharmaceuticals that have been detected in tap water at low doses. Analysis of atenolol, caffeine, erythromycin, carbamazepine and their metabolites in blood, urine, feces, fat tissue, liver and kidney after exposure to a mixture of these pharmaceuticals in treated drinking water were performed. The effects of this exposure were assessed in rats by measuring biochemical markers of organs injury or dysfunction. Simultaneously, the selected pharmaceuticals were also quantified in both physiological fluids and organ homogenates by liquid chromatography/tandem mass spectrometry (performed in multiple reaction monitoring mode and full scan mode). Following exposure of rats to a concentration of a pharmaceutical, which was ten times higher than the concentration known to be present in tap water, trace levels of some pharmaceuticals and their metabolites were detected in biological samples. This exposure did, however, not lead to significant organ injury/ dysfunction. Thus, we report here an experimental model that can be used to characterize the safety profile of pharmaceuticals in treated drinking water using a multiorgan toxicity approach.

http://www.ncbi.nlm.nih.gov/pubmed/27061931

“Pharmaceuticals and personal care products (PPCPs) are emerging chemicals of concern detected in surface waters globally.”

Environmental Toxicology And Chemistry • April 2016

Pharmaceutical concentrations in screened municipal wastewaters in Victoria, British Columbia: A comparison with prescription rates and predicted concentrations

Saunders LJ1, Mazumder A2, Lowe CJ2,3.

Abstract

Pharmaceuticals and personal care products (PPCPs) are emerging chemicals of concern detected in surface waters globally. Recent reviews advocate that PPCP occurrence, fate, and exposure need to be better predicted and characterized. The use of pharmaceutical prescription rates to estimate PPCP concentrations in the environment has been suggested. Concentrations of 7 pharmaceuticals (acetylsalicylic acid, diclofenac, fenoprofen, gemfibrozil, ibuprofen, ketoprofen, and naproxen) were measured in municipal wastewater using gas chromatography/ion trap-tandem mass spectroscopy (GC/IT-MS/MS). Sub-regional pharmaceutical prescription data were investigated to determine whether they could predict measured effluent concentrations (MECs) in wastewaters. Predicted effluent concentrations (PECs) for 5 of the 7 pharmaceuticals were within 2-fold agreement of the MECs when the fraction of parent pharmaceutical excreted was not considered. When the fraction of parent pharmaceutical excreted was considered, the respective PECs decreased, and most were within an order of magnitude of the MECs. Regression relationships of monthly PECs versus MECs were statistically significant ($p < 0.05$) but weak ($R(2) = 0.18$-0.56) for all pharmaceuticals except ketoprofen. This suggests high variability in the data and may be the result of factors influencing MECs such as the analytical methods used, wastewater sampling frequency, and methodology. The PECs were based solely on prescription rates and did not account for inputs of pharmaceuticals that had a significant over-the-counter component or were from other sources (e.g., hospitals).

http://www.ncbi.nlm.nih.gov/pubmed/26363402

“... in water C there was an alteration of sex ratio towards females, although in this case the alteration was reversible. A transgenerational alteration in the germ-line via an epigenetic mechanism from the previous generation is proposed as the most plausible explanation of this effect.”

Zygote • May 2016

Zebrafish as a possible bioindicator of organic pollutants in drinking waters with effects on reproduction: are effects cumulative or reversible?

Author information

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Abstract

Organic pollutants are present in drinking waters due to inefficient detection and removal treatments. For this reason, zebrafish is proposed as a complementary indicator in conventional potabilization treatments. Based on the most sensitive parameters detected in our previous work, in this study we attempted to examine the possible cumulative effect between generations of environmental pollutants likely present in drinking waters, when specimens were cultured in the same water and/or the possible reversibility of these effects when cultured in control water. To this end, embryos with the chorion intact were cultured in three drinking waters from different sources and in one control water for up to 5 months in 20 l glass tanks. Four replicates were performed in all water groups. Results in water group C (tap water from a city also located in a region with intensive agricultural activity, but from the hydrological basin of the river Xúquer) revealed a non-reversible effect on fertility rate. Also in water C there was an alteration of sex ratio towards females, although in this case the alteration was reversible. A transgenerational alteration in the germ-line via an epigenetic mechanism from the previous generation is proposed as the most plausible explanation of this effect.

http://www.ncbi.nlm.nih.gov/pubmed/27140034

“The removal effects of the membrane bioreactor seeded with aerobic granular sludge on five pharmaceuticals and personal care products varied. Using the membrane bioreactor seeded with aerobic granular sludge, the removal rates of prednisolone, naproxen and norfloxacin were 98.56, 84.02 and 87.85%, respectively. The removal rates of sulfamethoxazole and ibuprofen were 77.83 and 63.32%, respectively.”

Applied Microbiology And Biotechnology • January 2015

Microbial community structure and pharmaceuticals and personal care products removal in a membrane bioreactor seeded with aerobic granular sludge

Author information

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Abstract

A process involving the use of membrane bioreactor seeded with aerobic granular sludge (GMBR) was applied to the treatment of sewage containing pharmaceuticals and personal care products (PPCPs). The removal effects of five kinds of medicines in the reactor were investigated, and the microbial communities were constructed by polymerase chain reaction and denaturing gradient gel electrophoresis. We also determined the effects of different sludge retention and hydraulic retention times (SRT and HRT, respectively) and influent organic loading on GMBR’s efficiency in processing sewage containing PPCPs. The removal effects of the GMBR on five PPCPs varied. Using the GMBR, the removal rates of prednisolone, naproxen and norfloxacin were 98.56, 84.02 and 87.85%, respectively. The removal rates of sulfamethoxazole and ibuprofen were 77.83 and 63.32%, respectively. In the system, PPCP drugs had relatively less effect on microbial diversity. A certain succession was observed in the structural variation of microbial species in the GMBR. Microorganisms that can degrade PPCPs gradually accumulated, and antibiotic-resistant microorganisms, such as Firmicutes sp., Aeromonas sp. and Nitrospira sp., served a key function in the treatment of sewage containing antibiotics. Long SRT and HRT during the GMBR process can facilitate the removal of most PPCPs. The system efficiently removed PPCPs at high influent organic loading.

http://www.ncbi.nlm.nih.gov/pubmed/25099174

“The granular sludge effectively removed some but not all of the pharmaceuticals and personal care products tested; removal correlated with the microbial profiles in the granules, as assessed using Solexa sequencing technology. Sequencing revealed the presence of five phylogenetic groups: Proteobacteria, Bacteroidetes, Betaproteobacteria, an unclassified genus, and Zoogloea. The results demonstrated changes in the microbial profiles with time in response to the presence of pharmaceuticals and personal care products.”

Bioresource Technology • January 2015

Remediation of pharmaceuticals and personal care products using an aerobic granular sludge sequencing bioreactor and microbial community profiling using Solexa sequencing technology analysis

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Abstract

Recently, a new type of organic pollution derived from pharmaceuticals and personal care products (PPCPs) is gradually on the rise. Wastewater treatment to remove PPCPs was investigated using an aerobic granular sludge sequencing bioreactor (GSBR). After optimization of influent organic load, hydraulic shear stress, sludge settling time, etc., aerobic granular sludge was analyzed for its physiological and biochemical characteristics and tested for its efficacy to remove PPCPs wastewater. The granular sludge effectively removed some but not all of the PPCPs tested; removal correlated with the microbial profiles in the granules, as assessed using Solexa sequencing technology. Sequencing revealed the presence of five phylogenetic groups: Proteobacteria, Bacteroidetes, Betaproteobacteria, an unclassified genus, and Zoogloea. The results demonstrated changes in the microbial profiles with time in response to the presence of PPCPs. The effects of PPCPs on microbial communities in granular sludge process are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/25531682

“Ibuprofen was found to be the highest concentration pharmaceutical during Drinking Water Treatment Plant, up to 53.30 ng/L. Drinking Water Treatment Plant shows a positive effect on the removal of most pharmaceuticals with 81.2-99.5 % removal efficiencies, followed by carbamazepine with 55.4 % removal efficiency, **but it has no effect for removing ibuprofen and bezafibrate.**”

Environmental Science And Pollution Researxh International • February 2015

Determination of selected pharmaceuticals in tap water and drinking water treatment plant by high-performance liquid chromatography-triple quadrupole mass spectrometer in Beijing, China

Author information

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Abstract

A simultaneous determination method of 14 multi-class pharmaceuticals using solid-phase extraction (SPE) followed by high-performance liquid chromatography-tandem mass spectrometer (HPLC-MS/MS) was established to measure the occurrence and distribution of these pharmaceuticals in tap water and a drinking water treatment plant (DWTP) in Beijing, China. Target compounds included seven anti-inflammatory drugs, two antibacterial drugs, two lipid regulation drugs, one antiepileptic drug, and one hormone. Limits of detection (LODs) and limits of quantitation (LOQs) ranged from 0.01 to 1.80 ng/L and 0.05 to 3.00 ng/L, respectively. Intraday and inter-day precisions, recoveries of different matrices, and matrix effects were also investigated. Of the 14 pharmaceutical compounds selected, nine were identified in tap water of Beijing downtown with the concentration up to 38.24 ng/L (carbamazepine), and the concentration levels of detected pharmaceuticals in tap water (<5 ng/L for most pharmaceuticals) were lower than previous studies in other countries. In addition, ten and six pharmaceuticals were measured in raw water and finished water at the concentration ranged from 0.10 to 16.23 and 0.13 to 17.17 ng/L, respectively. Five compounds were detected most frequently in DWTP, namely antipyrine, carbamazepine, isopropylantipyrine, aminopyrine, and bezafibrate. Ibuprofen was found to be the highest concentration pharmaceutical during DWTP, up to 53.30 ng/L. DWTP shows a positive effect on the removal of most pharmaceuticals with 81.2-99.5 % removal efficiencies, followed by carbamazepine with 55.4 % removal efficiency, but it has no effect for removing ibuprofen and bezafibrate.

http://www.ncbi.nlm.nih.gov/pubmed/25196960

“Pharmaceuticals and personal care products (PPCPs) along with illicit drugs (IDs) are newly recognized classes of environmental pollutants and are receiving considerable attention because of their environmental impacts: frequent occurrence, persistence and risk to aquatic life and humans. However, relatively little information is often available with regard to their possible biotic and abiotic transformation products (TPs).”

Science And The Total Environment • February 2015

Occurrence and removal of transformation products of PPCPs and illicit drugs in wastewaters: a review

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Abstract

Pharmaceuticals and personal care products (PPCPs) along with illicit drugs (IDs) are newly recognized classes of environmental pollutants and are receiving considerable attention because of their environmental impacts: frequent occurrence, persistence and risk to aquatic life and humans. However, relatively little information is often available with regard to their possible biotic and abiotic transformation products (TPs). This lack of knowledge has resulted in a substantial amount of ongoing effort to develop methods and approaches that would assess their occurrence, degradability potential elimination mechanisms and efficiencies in sewage treatment plants as well as environmental and human health risks. In this article, an extensive literature survey was performed in order to present the current stage of knowledge and progress made in the occurrence of TPs of PPCPs and IDs in raw and treated wastewaters. Apart from the TPs resulting from structural transformations of the parent compound in the aquatic environment or in technological treatment facilities (e.g. sewage and drinking water treatment plants), free metabolites and drug conjugates formed during human metabolism have also been included in this review as they are also released into the aquatic environment through wastewaters. Their concentration levels were reported in influents and effluents of WWTPs, hospital effluents and their removals in the treatment plants were discussed. Finally, information on the toxicity of TPs has been compiled when available.

http://www.ncbi.nlm.nih.gov/pubmed/25461093

Water Research • March 2015

Comprehensive study of the antidiabetic drug metformin and its transformation product guanylurea in Greek wastewaters

Author information

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Abstract

“Many pollutants such as pharmaceuticals and their transformation products (TPs) are not efficiently removed from wastewater treatment plants and enter into surface waters. The aim of this study was to investigate the occurrence and behavior of metformin, one of the most prescribed drugs worldwide, and its biological transformation product guanylurea, in eight wastewater treatment plants (WWTPs) of Greece. All WWTPs were equipped with conventional activated sludge treatment and the samples were taken from the influents and the effluents, over the four seasons of one year. The analytical method developed based on SPE followed by LC-UV/Vis-ESI/MS analysis, while positive findings were confirmed also by means of LTQ Orbitrap mass spectrometer. High polarity of both compounds led to the extraction with Oasis HLB and the use of the anionic surfactant SDS. The results showed that metformin dominated in the influents (bql-1167 ng/L), while guanylurea in the effluents (bql-627 ng/L) of the wastewater treatment plants, with Metformin/Guanylurea ratio ranging between 0.88 and 81.3 in the influents and between 0.005 and 0.78 in the effluents. Lack of a clear seasonal tendency in the occurrence and removal or formation was observed. Finally, an ecotoxicological risk assessment of metformin in effluent wastewaters took place by calculating the ratio between the environmental concentrations (MEC) and the predicted no effect concentrations (PNEC). Despite the fact that metformin presented low risk in all cases, an environmental concern is suspected for guanylurea since it is continuously released into the aquatic environment.”

http://www.ncbi.nlm.nih.gov/pubmed/25562582

“The photochemical transformation of widely used cosmetic preservatives including benzoates, parabens, BHA, BHT and triclosan ... were detected in aqueous photodegradation experiments, being tentatively identified based on their mass spectra. The photoformation of unexpected photoproducts such as 2- and 4-hydroxybenzophenones, and 2,8-dichlorodibenzo-p-dioxin in PCPs are reported in this work for the first time.”

Journal Of Chromatography • April 2015

Identification of unwanted photoproducts of cosmetic preservatives in personal care products under ultraviolet-light using solid-phase microextraction and micro-matrix solid-phase dispersion

Author information

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Abstract

The photochemical transformation of widely used cosmetic preservatives including benzoates, parabens, BHA, BHT and triclosan has been investigated in this work applying an innovative double-approach strategy: identification of transformation products in aqueous photodegradation experiments (UV-light, 254nm), followed by targeted screening analysis of such photoproducts in UV-irradiated cosmetic samples. Solid-phase microextraction (SPME) was applied, using different fiber coatings, in order to widen the range of detectable photoproducts in water, whereas UV-irradiated personal care products (PCPs) containing the target preservatives were extracted by micro-matrix solid-phase dispersion (micro-MSPD). Both SPME and micro-MSPD-based methodologies were successfully optimized and validated. Degradation kinetics of parent species, and photoformation of their transformation by-products were monitored by gas chromatography coupled to mass spectrometry (GC-MS). Thirty nine photoproducts were detected in aqueous photodegradation experiments, being tentatively identified based on their mass spectra. Transformation pathways between structurally related by-products, consistent with their kinetic behavior were postulated. The photoformation of unexpected photoproducts such as 2- and 4-hydroxybenzophenones, and 2,8-dichlorodibenzo-p-dioxin in PCPs are reported in this work for the first time.

http://www.ncbi.nlm.nih.gov/pubmed/25757820

Water Research • April 2015

A pilot study on the assessment of trace organic contaminants including pharmaceuticals and personal care products from on-site wastewater treatment systems along Skaneateles Lake in New York State, USA

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Abstract

On-site wastewater treatment systems (OWTSs or septic systems) are designed to treat and dispose effluents on the same property that produces the wastewater. Approximately 25% of the U.S. population is served by such facilities. Nevertheless, studies on the treatment efficiency and discharge of organic contaminants through septic effluents are lacking. This pilot study showed the occurrence of organic contaminants including pharmaceuticals and personal care products (PPCPs), perfluoroalkyl surfactants (PFASs), polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs) in septic effluents, adjacent lake water samples, household drinking water in homes that use lake water or a well adjacent to the lake as a source of drinking water, and offshore lake water samples. Septic effluent as well as lake and tap water samples were collected from several households with OWTSs around Skaneateles Lake located in central New York. The advanced on-site systems were installed in some households for the purpose of limiting nutrient levels in the effluent to protect the local surface water. Additionally, because many of these systems serve homes with limited land, advanced treatment systems were needed. The median concentrations of ten PPCPs (ranged from 0.45 to 388 ng/L) and eleven PFASs (ranged from 0.20 to 14.6 ng/L) in septic water were significantly higher ($p \leq 0.01$) than in lake water samples. The median concentrations of PPCPs and PFASs in lake and tap water samples were not significantly different ($p \geq 0.65$). The median concentrations of ∑PBDEs in septic, lake, and tap water samples were 7.47, 3.49, and 2.22 ng/L, respectively, and those for ∑PCBs were 33.1, 29.2, and 28.6 ng/L, respectively. The mass flux of PPCPs (i.e. the mass flow of PPCPs per unit area per unit time) through the disposal of treated septic effluent from textile biofilter and aerobic treatments to the dispersal unit ranged from 12 (carbamazepine) to 66900 μg/m(2)/day (caffeine) whereas that for PFASs ranged from 7.0 (perfluorobutanesulfonate) to 833 μg/m(2)/day (perfluorooctanoic acid). Based on the ratio of measured concentrations and method detection limit, triclocarban, perfluorooctanoic acid, and perfluorooctanesulfonate have the potential to be used as chemical tracers of septic water contamination in Skaneateles Lake. The median concentrations of atenolol, a beta-blocker drug, in septic water were significantly correlated with enterococci counts.

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“Pharmaceuticals are becoming widely distributed in waters and wastewaters and pose a serious threat to public health. The present study aimed to analyze non-steroidal anti-inflammatory drugs (NSAIDs) in surface waters, drinking water, and wastewater in Tehran, Iran.”

Environmental Monitoring And Assessment • December 2015

Occurrence of non-steroidal anti-inflammatory drugs in Tehran source water, municipal and hospital wastewaters, and their ecotoxicological risk assessment

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Abstract

Pharmaceuticals are becoming widely distributed in waters and wastewaters and pose a serious threat to public health. The present study aimed to analyze non-steroidal anti-inflammatory drugs (NSAIDs) in surface waters, drinking water, and wastewater in Tehran, Iran. Thirty-six samples were collected from surface waters, tap water, and influent and effluent of municipal and hospital wastewater treatment plants (WWTP). A solid-phase extraction (SPE) followed by liquid chromatography-tandem mass spectrometry method was used for the determination of pharmaceuticals, namely ibuprofen (IBP), naproxen (NPX), diclofenac (DIC), and indomethacin (IDM). IBP was found in most of the samples and had the highest concentration. The highest concentrations of NSAIDs were found in the municipal WWTP influents and hospital WWTP effluents. In the municipal WWTP influent samples, the concentrations of IBP, NPX, DIC, and IDM were 1.05, 0.43, 0.23, and 0.11 µg/L, respectively. DIC was found only in one river sample. All NSAIDs were detected in tap water samples. However, their concentration was very low and the maximum values for IBP, NPX, DIC, and IDM were 47, 39, 24, and 37 ng/L, respectively, in tap water samples. Results showed that the measured pharmaceuticals were detected in all rivers with low concentrations in nanograms per liter range, except DIC which was found only in one river. Furthermore, this study showed that the aforementioned pharmaceuticals are not completely removed during their passage through WWTPs. A potential environmental risk of selected NSAIDs for the urban wastewater has been discussed. However, given their low measured concentrations, no ecotoxicological effect is suspected to occur.

http://www.ncbi.nlm.nih.gov/pubmed/26553436

“The results showed the occurrence of all target compounds in the wastewater samples with concentrations up to 96.65 μg/L. Paracetamol, caffeine, trimethoprim, sulfamethoxazole, carbamazepine, diclofenac and salicylic acid were the dominant compounds, while tolfenamic acid, fenofibrate and simvastatin were the less frequently detected compounds ...”

Science Of The Total Environment • January 2014

Investigation of PPCPs in wastewater treatment plants in Greece: occurrence, removal and environmental risk assessment

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Abstract

In the present work, an extensive study on the presence of eighteen pharmaceuticals and personal care products (PPCPs) in eight wastewater treatment plants (WWTPs) of Greece has been conducted. The study covered four sampling periods over 1-year, where samples (influents; effluents) from eight WWTPs of various cities in Greece were taken. All WWTPs investigated are equipped with conventional activated sludge treatment. A common pre-concentration step based on SPE was applied, followed by LC-UV/Vis-ESI-MS. Further confirmation of positive findings was accomplished by using LC coupled to a high resolution Orbitrap mass spectrometer. The results showed the occurrence of all target compounds in the wastewater samples with concentrations up to 96.65 μg/L. Paracetamol, caffeine, trimethoprim, sulfamethoxazole, carbamazepine, diclofenac and salicylic acid were the dominant compounds, while tolfenamic acid, fenofibrate and simvastatin were the less frequently detected compounds with concentrations in effluents below the LOQ. The removal efficiencies showed that many WWTPs were unable to effectively remove most of the PPCPs investigated. Finally, the study provides an assessment of the environmental risk posed by their presence in wastewaters by means of the risk quotient (RQ). RQs were more than unity for various compounds in the effluents expressing possible threat for the aquatic environment. Triclosan was found to be the most critical compound in terms of contribution and environmental risk, concluding that it should be seriously considered as a candidate for regulatory monitoring and prioritization on a European scale on the basis of realistic PNECs. The results of the extensive monitoring study contributed to a better insight on PPCPs in Greece and their presence in influent and effluent wastewaters. Furthermore, the unequivocal identification of two transformation products of trimethoprim in real wastewaters by using the advantages of the LTQ Orbitrap capabilities provides information that should be taken into consideration in future PPCP monitoring studies in wastewaters.

http://www.ncbi.nlm.nih.gov/pubmed/23933429

Marine Pollution Bulletin • August 2014

Polar organic micropollutants in the coastal environment of different marine systems

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Abstract

“Polar anthropogenic organic micropollutants are frequently detected in freshwater and discharged on large scale into marine systems. In this work the results of 153 samples collected from the shorelines of the Baltic Sea (Germany), Northern Adriatic Sea (Italy), Aegean Sea and Dardanelles (Greece & Turkey), San Francisco Bay (USA), Pacific Ocean (USA), Mediterranean Sea (Israel), and Balearic Sea (Spain) are presented. The samples were analyzed for various classes of micropollutants such as pharmaceuticals, corrosion inhibitors, biocides, and stimulants. Caffeine, paraxanthine, theobromine, tolyltriazole, 1H-benzotriazole, and atrazine were detected in>50% of all samples. The detection frequencies of carbamazepine, iopamidol, diuron, sulfamethoxazole, paracetamol, theophylline, and atenolol were between 20% and 32%. As caffeine is linked to untreated wastewater, the widespread occurrence of raw sewage in marine environments and thus potentially elevated nutrient concentrations and risk for the presence of wastewater-related pathogens is remarkable.”

http://www.ncbi.nlm.nih.gov/pubmed/24686145

“The efficiency of biological removal of pharmaceuticals and personal care products was found to be dependent on the concentration at which the contamination occurs for some, but not all, pharmaceuticals and personal care products.”

Applied Environmental Microbiology • April 2014

Removal of pharmaceuticals and personal care products during water recycling: microbial community structure and effects of substrate concentration

Author information

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Abstract

Many pharmaceuticals and personal care products (PPCPs) have been shown to be biotransformed in water treatment systems. However, little research exists on the effect of initial PPCP concentration on PPCP biotransformation or on the microbial communities treating impacted water. In this study, biological PPCP removal at various concentrations was assessed using laboratory columns inoculated with wastewater treatment plant effluent. Pyrosequencing was used to examine microbial communities in the columns and in soil from a soil aquifer treatment (SAT; a method of water treatment prior to reuse) site. Laboratory columns were supplied with different concentrations (0.25, 10, 100, or 1,000 µg liter(-1)) of each of 15 PPCPs. Five PPCPs (4-isopropyl-3-methylphenol [biosol], p-chloro-m-xylenol, gemfibrozil, ketoprofen, and phenytoin) were not removed at any tested concentrations. Two PPCPs (naproxen and triclosan) exhibited removals independent of PPCP concentration. PPCP removal efficiencies were dependent on initial concentrations for biphenylol, p-chloro-m-cresol, chlorophene, diclofenac, 5-fluorouracil, ibuprofen, and valproic acid, showing that PPCP concentration can affect biotransformation. Biofilms from sand samples collected from the 0.25- and 10-µg liter(-1) PPCP columns were pyrosequenced along with SAT soil samples collected on three consecutive days of a wetting and drying cycle to enable comparison of these two communities exposed to PPCPs. SAT communities were similar to column communities in taxonomy and phylotype composition, and both were found to contain close relatives of known PPCP degraders. The efficiency of biological removal of PPCPs was found to be dependent on the concentration at which the contamination occurs for some, but not all, PPCPs.

Full Report with References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3993184/

“Mineral and tap waters also presented significant amounts (approx. 100ngL(-1)) of ibuprofen, naproxen, propylparaben and butylparaben. The occurrence at trace levels of several PPCPs in drinking water raises concerns about possible implications for human health.”

Science And The Total Environment • June 2014

Occurrence of acidic pharmaceuticals and personal care products in Turia River Basin: from waste to drinking water

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Abstract

The occurrence of 21 acidic pharmaceuticals, including illicit drugs, and personal care products (PPCPs) in waste, surface and drinking water and in sediments of the Turia River Basin (Valencia, Spain) was studied. A liquid chromatography tandem mass spectrometry (LC-MS/MS) method was developed for the determination of these PPCPs with electrospray (ESI) in negative ionization (NI) mode. Ammonium fluoride in the mobile phase improved ionization efficiency by an average increase in peak area of 5 compared to ammonium formate or formic acid. All studied compounds were detected and their concentration was waste water>surface water>drinking water. PPCPs were in waste water treatment plants (WWTPs) influents up to 7.26µgL(-1), dominated by ibuprofen, naproxen and 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCOOH). WWTPs were highly effective in removing most of them, with an average removal rate of >90%. PPCPs were still detected in effluents in the 6.72-940ngL(-1) range, with the THCOOH, triclocarban, gemfibrozil and diclofenac as most prevalent. Similarly, diclofenac, gemfibrozil, ibuprofen, naproxen and propylparaben were detected quite frequently from the low ngL(-1) range to 7µgL(-1) in the surface waters of Turia River. Ibuprofen, methylparaben, salicylic acid and tetrahydrocannabinol (THC) were at concentrations up to 0.85ngg(-1) d.w. in sediments. The discharge of WWTP as well as of non-treated waters to this river is a likely explanation for the significant amount of PPCPs detected in surface waters and sediments. Mineral and tap waters also presented significant amounts (approx. 100ngL(-1)) of ibuprofen, naproxen, propylparaben and butylparaben. The occurrence at trace levels of several PPCPs in drinking water raises concerns about possible implications for human health.

http://www.ncbi.nlm.nih.gov/pubmed/24686145

“The presence of antidepressants in drinking water and the aquatic environment could have long-term effects even at low exposure level, especially since **synergy** amongst pharmaceutical pollutants may occur.”

Ecotoxicology And Environmental Safety • July 2014

Occurrence of antidepressant residues in the sewage-impacted Vistula and Utrata rivers and in tap water in Warsaw (Poland)

Author information

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Abstract

Antidepressants, even at low concentrations, can reveal some adverse effects on aquatic life due to disturbing homeostasis throughout the central and peripheral nervous system both in vertebrates and invertebrates. To date there have not been any reports regarding the presence of these pharmaceuticals in surface and tap waters in Eastern Europe. Therefore the aim of this study was to determine the presence of 21 antidepressant pharmaceuticals at specific points of the main Polish river - the Vistula, a smaller river of the Warsaw region - the Utrata, as well as in tap water samples of Warsaw. Samples were collected twice at one month intervals and analysed using solid-phase extraction (SPE) technique coupled with the liquid chromatography-electrospray ionisation-tandem mass spectrometer (LC-MS/MS) method operated under the multiple reaction monitoring mode (MRM). This is the first study where active compounds such as moclobemid or trazodone in the environment have been investigated. Environmental risk assessment of antidepressants in Poland was estimated on the basis of annuals sale data extracted from the NFZ (Narodowy Fundusz Zdrowia-National Health Service) base of reimbursed pharmaceuticals(1). Predicted environmental concentration (PEC) of target pharmaceuticals were compared with their measured concentration (MEC). Moreover, the application of the EMEA/CHMP guideline for environmental risk assessment of the antidepressants was discussed. The highest concentration of antidepressants was observed in the small river Utrata. In tap water only trace amounts of antidepressants including citalopram (up to 1.5ng/l), mianserin (up to 0.9ng/l), sertraline (<3.1ng/l), moclobemid (up to 0.3ng/l) and venlafaxine (up to 1.9ng/l) were detected. However this highlights their inadequate elimination in the drinking waste treatment facility. The presence of antidepressants in drinking water and the aquatic environment could have long-term effects even at low exposure level, especially since synergy amongst pharmaceutical pollutants may occur.

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Marine Pollution Bulletin • August 2014

Polar organic micropollutants in the coastal environment of different marine systems

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Abstract

“Polar anthropogenic organic micropollutants are frequently detected in freshwater and discharged on large scale into marine systems. In this work the results of 153 samples collected from the shorelines of the Baltic Sea (Germany), Northern Adriatic Sea (Italy), Aegean Sea and Dardanelles (Greece & Turkey), San Francisco Bay (USA), Pacific Ocean (USA), Mediterranean Sea (Israel), and Balearic Sea (Spain) are presented. The samples were analyzed for various classes of micropollutants such as pharmaceuticals, corrosion inhibitors, biocides, and stimulants. Caffeine, paraxanthine, theobromine, tolyltriazole, 1H-benzotriazole, and atrazine were detected in>50% of all samples. The detection frequencies of carbamazepine, iopamidol, diuron, sulfamethoxazole, paracetamol, theophylline, and atenolol were between 20% and 32%. As caffeine is linked to untreated wastewater, the widespread occurrence of raw sewage in marine environments and thus potentially elevated nutrient concentrations and risk for the presence of wastewater-related pathogens is remarkable.”

http://www.ncbi.nlm.nih.gov/pubmed/25015017

“This work analyzes the seasonal variation (winter and summer) of ten drugs of abuse, six metabolites and three benzodiazepines in surface waters from the Jarama and Manzanares Rivers in the Madrid Region, the most densely populated area in Spain. The occurrence of these compounds in tap water in this region is also investigated and a preliminary human health risk characterization performed for those substances found in tap water. Finally, a screening level risk assessment that combines the measured environmental concentrations (MECs) with dose-response data to estimate Hazard Quotients (HQs) for the compounds studied is also presented.”

Environment International • September 2014

Drugs of abuse and benzodiazepines in the Madrid Region (Central Spain): seasonal variation in river waters, occurrence in tap water and potential environmental and human risk

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Abstract

This work analyzes the seasonal variation (winter and summer) of ten drugs of abuse, six metabolites and three benzodiazepines in surface waters from the Jarama and Manzanares Rivers in the Madrid Region, the most densely populated area in Spain. The occurrence of these compounds in tap water in this region is also investigated and a preliminary human health risk characterization performed for those substances found in tap water. Finally, a screening level risk assessment that combines the measured environmental concentrations (MECs) with dose-response data to estimate Hazard Quotients (HQs) for the compounds studied is also presented. The results of this study show the presence of fourteen out of the nineteen compounds analyzed in winter and twelve of them in summer. The most ubiquitous compounds, with a frequency of detection of 100% in both seasons, were the cocaine metabolite benzoylecgonine (BE), the amphetamine-type stimulant (ATS) ephedrine (EPH), the opioid methadone (METH), the METH metabolite 2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and the three benzodiazepines investigated, namely alprazolam (ALP), diazepam (DIA) and lorazepam (LOR). The highest concentrations observed corresponded to EPH (1020ngL(-1) in winter and 250ngL(-1) in summer). The only compounds not detected in both seasons were heroin (HER) and its metabolite 6-acetylmorphine (6ACM), lysergic acid diethylamide (LSD) and its metabolite 2-oxo-3-hydroxy-LSD (O-H-LSD), and Δ(9)-tetrahydrocannabinol (THC). In terms of overall concentration, all sampling points presented higher concentrations in winter than in summer. Statistical analyses performed to gather evidence concerning occasional seasonal differences in the concentrations of individual substances between summer and winter showed statistically significantly higher concentrations ($p<0.05$) of BE, EPH and the opioid morphine (MOR) in winter than in summer. Two out of the nineteen compounds studied, namely cocaine (CO) and EPH, were detected in tap water from one sampling point at concentrations of 1.61 and 0.29ngL(-1), respectively. The preliminary human health risk characterization showed that no toxic effects could be expected at the detected concentration level in tap water. The screening level risk assessment showed that MOR, EDDP and the THC metabolite 11-nor-9-carboxy-Δ(9)-tetrahydrocannabinol (THC-COOH) were present in at least one of the sampling sites in a concentration leading to a Hazard Quotient (HQ) value between 1.0 and 10.0, thus indicating some possible adverse effects. The cumulative HQ or Toxic units (TUs) calculated for each of the groups studied showed that opioids and cannabinoids were present at concentrations high enough to potentially generate some adverse effects on at least one sampling point.

http://www.ncbi.nlm.nih.gov/pubmed/24908641

“The study shows that pharmaceuticals originating from wastewater treatment plant effluents can be traced to the bile of wild bream and roach living in a lake where diclofenac, naproxen, and ibuprofen are present as pollutants.”

Environmental Science Technology • January 2013

The anti-inflammatory drugs diclofenac, naproxen and ibuprofen are found in the bile of wild fish caught downstream of a wastewater treatment plant

Author information

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Abstract

Pharmaceutical residues are ubiquitous in rivers, lakes, and at coastal waters affected by discharges from municipal wastewater treatment plants. In this study, the presence of 17 different pharmaceuticals and six different phase I metabolites was determined in the bile of two wild fish species, bream (Abramis brama) and roach (Rutilus rutilus). The fish were caught from a lake that receives treated municipal wastewater via a small river. Prior to analyses, the bile content was enzymatically hydrolyzed to convert the glucuronide metabolites into the original pharmaceuticals or phase I metabolites. The solid phase extracts of hydrolyzates were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) in the multiple reaction monitoring mode. The anti-inflammatory drug naproxen could be detected in all the six bream and roach bile samples. Diclofenac was found in five of the bream and roach samples, while ibuprofen was detected in three bream and two roach samples. The observed bile concentrations of diclofenac, naproxen, and ibuprofen in bream ranged from 6 to 95 ng mL(-1), 6 to 32 ng mL(-1), and 16 to 34 ng mL(-1), respectively. The corresponding values in roach samples ranged from 44 to 148 ng mL(-1), 11 to 103 ng mL(-1) and 15 to 26 ng mL(-1), respectively. None of the other studied compounds could be detected. The study shows that pharmaceuticals originating from wastewater treatment plant effluents can be traced to the bile of wild bream and roach living in a lake where diclofenac, naproxen, and ibuprofen are present as pollutants.

http://www.ncbi.nlm.nih.gov/pubmed/23186122

Marine Pollution Bulletin • May 2013

Twenty years later—atrazine concentrations in selected coastal waters of the Mediterranean and the Baltic Sea

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Abstract

“Despite its EU-wide ban in 2004 the triazine herbicide atrazine (ATR) and its transformation products (TPs) are frequently detected in the aqueous environment. In this study, concentrations of ATR, two of its TPs, and terbuthylazine (TERB) are presented and discussed in coastal waters of the Northern Aegean Sea, the Dardanelles, the Baltic Sea (Germany), the Northern Adriatic Sea (Italy), and the coastline close to Barcelona (Spain). The water samples (n=132) were taken in 2009-2011. Sediment samples (n=7) were taken from Baltic Sea (Germany) and Thermaikos Gulf (Greece). Maximum ATR concentrations (31-41 ng Lß) were detected in Istanbul and the Dardanelles. A concentration gradient from East to West in the Aegean Sea was observed, indicating ongoing ATR contamination via the Dardanelles. Low concentrations and detection frequencies were observed at the other locations, indicating the success of the prohibition. However, the presence of TERB in the Northern Adriatic Sea raises concern.”

http://www.ncbi.nlm.nih.gov/pubmed/23481690

“Current treatment methods, however, do not seem to be efficient since organic pollutants were detected in significant concentrations in purified tap water.”

Environmental Science And Pollution Research International • October 2013

Occurrence and distribution of organic trace substances in waters from the Three Gorges Reservoir, China

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Abstract

This study deals with the evaluation of water quality of the Three Gorges Reservoir (TGR) in order to assess its suitability as a raw water source for drinking water production. Therefore, water samples from (1) surface water, (2) tap water, and (3) wastewater treatment plant effluents were taken randomly by 2011-2012 in the area of the TGR and were analyzed for seven different organic contaminant groups (207 substances in total), applying nine different analytical methods. In the three sampled water sources, typical contaminant patterns were found, i.e., pesticides and polycyclic aromatic hydrocarbons (PAH) in surface water with concentrations of 0.020-3.5 µg/L and 0.004-0.12 µg/L, disinfection by-products in tap water with concentrations of 0.050-79 µg/L, and pharmaceuticals in wastewater treatment plant effluents with concentrations of 0.020-0.76 µg/L, respectively. The most frequently detected organic compounds in surface water (45 positives out of 57 samples) were the pyridine pesticides clopyralid and picloram. The concentrations might indicate that they are used on a regular basis and in conjunction in the area of the TGR. Three- and four-ring PAH were ubiquitously distributed, while the poorly soluble five- and six-ring members, perfluorinated compounds, polychlorinated biphenyls, and polybrominated diphenyl ethers, were below the detection limit. In general, the detected concentrations in TGR are in the same range or even lower compared to surface waters in western industrialized countries, although contaminant loads can still be high due to a high discharge. With the exception of the two pesticides, clopyralid and picloram, concentrations of the investigated organic pollutants in TGR meet the limits of the Chinese Standards for Drinking Water Quality GB 5749 (Ministry of Health of China and Standardization Administration of China 2006) and the European Union (EU) Council Directive 98/83/EC on the quality of water intended for human consumption (The Council of the European Union 1998), or rather, the EU Directive on environmental quality standards in the field of water policy (The European Parliament and The Council of the European Union 2008). Therefore, the suggested use of surface water from TGR for drinking water purposes is a valid option. Current treatment methods, however, do not seem to be efficient since organic pollutants were detected in significant concentrations in purified tap water.

http://www.ncbi.nlm.nih.gov/pubmed/23832801

“The most relevant compounds in the effluent waters with the highest median concentration levels were the artificial sweeteners acesulfame and sucralose, benzotriazoles (corrosion inhibitors), several organophosphate ester flame retardants and plasticizers (e.g. tris(2-chloroisopropyl) phosphate; TCPP), pharmaceutical compounds such as carbamazepine, tramadol, telmisartan, venlafaxine, irbesartan, fluconazole, oxazepam, fexofenadine, diclofenac, citalopram, codeine, bisoprolol, eprosartan, the antibiotics trimethoprim, ciprofloxacine, sulfamethoxazole, and clindamycine, the insect repellent N,N’-diethyltoluamide (DEET), the pesticides MCPA and mecoprop, perfluoroalkyl substances (such as PFOS and PFOA), caffeine, and gadolinium.”

Water Research • November 2013

EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents

Author information
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Abstract

In the year 2010, effluents from 90 European wastewater treatment plants (WWTPs) were analyzed for 156 polar organic chemical contaminants. The analyses were complemented by effect-based monitoring approaches aiming at estrogenicity and dioxin-like toxicity analyzed by in vitro reporter gene bioassays, and yeast and diatom culture acute toxicity optical bioassays. Analyses of organic substances were performed by solid-phase extraction (SPE) or liquid-liquid extraction (LLE) followed by liquid chromatography tandem mass spectrometry (LC-MS-MS) or gas chromatography high-resolution mass spectrometry (GC-HRMS). Target microcontaminants were pharmaceuticals and personal care products (PPCPs), veterinary (antibiotic) drugs, perfluoroalkyl substances (PFASs), organophosphate ester flame retardants, pesticides (and some metabolites), industrial chemicals such as benzotriazoles (corrosion inhibitors), iodinated x-ray contrast agents, and gadolinium magnetic resonance imaging agents; in addition biological endpoints were measured. The obtained results show the presence of 125 substances (80% of the target compounds) in European wastewater effluents, in concentrations ranging from low nanograms to milligrams per liter. These results allow for an estimation to be made of a European median level for the chemicals investigated in WWTP effluents. The most relevant compounds in the effluent waters with the highest median concentration levels were the artificial sweeteners acesulfame and sucralose, benzotriazoles (corrosion inhibitors), several organophosphate ester flame retardants and plasticizers (e.g. tris(2-chloroisopropyl)phosphate; TCPP), pharmaceutical compounds such as carbamazepine, tramadol, telmisartan, venlafaxine, irbesartan, fluconazole, oxazepam, fexofenadine, diclofenac, citalopram, codeine, bisoprolol, eprosartan, the antibiotics trimethoprim, ciprofloxacine, sulfamethoxazole, and clindamycine, the insect repellent N,N’-diethyltoluamide (DEET), the pesticides MCPA and mecoprop, perfluoroalkyl substances (such as PFOS and PFOA), caffeine, and gadolinium.

http://www.ncbi.nlm.nih.gov/pubmed/24091184

Reviews In Environmental Contamination And Toxicology • January 2011

Illicit drugs: contaminants in the environment and utility in forensic epidemiology

By C.G. Daughton

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Abstract

The published literature that addresses the many facets of pharmaceutical ingredients as environmental contaminants has grown exponentially since the 1990s. Although there are several thousand active ingredients used in medical pharmaceuticals worldwide, illicit drug ingredients (IDIs) have generally been excluded from consideration. Medicinal and illicit drugs have been treated separately in environmental research even though they pose many of the same concerns regarding the potential for both human and ecological exposure. The overview presented here covers the state of knowledge up until mid-2010 regarding the origin, occurrence, fate, and potential for biological effects of IDIs in the environment. Similarities exist with medical pharmaceuticals, particularly with regard to the basic processes by which these ingredients enter the environment--excretion of unmetabolized residues (including via sweat), bathing, disposal, and manufacturing. The features of illicit drugs that distinguish them from medical pharmaceuticals are discussed. Demarcations between the two are not always clear, and a certain degree of overlap adds additional confusion as to what exactly defines an illicit drug; indeed, medical pharmaceuticals diverted from the legal market or used for non-medicinal purposes are also captured in discussions of illicit drugs. Also needing consideration as part of the universe of IDIs are the numerous adulterants and synthesis impurities often encountered in these very impure preparations. Many of these extraneous chemicals have high biological activity themselves. In contract to medical pharmaceuticals, comparatively little is know about the fate and effects of IDIs in the environment. Environmental surveys for IDIs have revealed their presence in sewage wastewaters, raw sewage sludge and processed sludge (biosolids), and drinking water. Nearly nothing is known, however, regarding wildlife exposure to IDIs, especially aquatic exposure such as indicated by bioconcentration in tissues. In contrast to pharmaceuticals, chemical monitoring surveys have revealed the presence of certain IDIs in air and monetary currencies--the latter being of interest for the forensic tracking of money used in drug trafficking. Another unknown with regard to IDIs is the accuracy of current knowledge regarding the complete scope of chemical identities of the numerous types of IDIs in actual use (particularly some of the continually evolving designer drugs new to forensic chemistry) as well as the total quantities being trafficked, consumed, or disposed. The major aspect unique to the study of IDI's in the environment is making use of their presence in the environment as a tool to obtain better estimates of the collective usage of illicit drugs across entire communities. First proposed in 2001, but under investigation with field applications only since 2005, this new modeling approach for estimating drug usage by monitoring the concentrations of IDIs (or certain unique metabolites) in untreated sewage has potential as an additional source of data to augment or corroborate the information-collection ability of conventional written and oral surveys of drug-user populations. This still evolving monitoring tool has been called "sewer epidemiology" but is referred to in this chapter by a more descriptive proposed term "FEUDS" (Forensic Epidemiology Using Drugs in Sewage). The major limitation of FEUDS surrounds the variables involved at various steps performed in FEUDS calculations. These variables are summarized and span sampling and chemical analysis to the final numeric calculations, which particularly require a better understanding of IDI pharmacokinetics than currently exists. Although little examined in the literature, the potential for abuse of FEUDS as a tool in law enforcement is briefly discussed. Finally, the growing interest in FEUDS as a methodological approach for estimating collective public usage of illicit drugs points to the feasibility of mining other types of chemical information from sewage. On the horizon is the potential for "sewage information mining" (SIM) as a general approach for measuring a nearly limitless array of biochemical markers that could serve as collective indicators of the specific or general status of public health or disease at the community-wide level. SIM may create the opportunity to view communities from a new perspective--"communities as the patient." This could potentially lead to the paradigm of combining human and ecological communities as a single patient--as an interconnected whole.

http://www.ncbi.nlm.nih.gov/pubmed/21170703

Water Research • February 2011

Investigation of pharmaceuticals in Missouri natural and drinking water using high performance liquid chromatography-tandem mass spectrometry

Author information
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Abstract

"A comprehensive method has been developed and validated in two different water matrices for the analysis of 16 pharmaceutical compounds using solid phase extraction (SPE) of water samples, followed by liquid chromatography coupled with tandem mass spectrometry. These 16 compounds include antibiotics, hormones, analgesics, stimulants, antiepileptics, and X-ray contrast media. Method detection limits (MDLs) that were determined in both reagent water and municipal tap water ranged from 0.1 to 9.9 ng/L. Recoveries for most of the compounds were comparable to those obtained using U.S. EPA methods. Treated and untreated water samples were collected from 31 different water treatment facilities across Missouri, in both winter and summer seasons, and analyzed to assess the 16 pharmaceutical compounds. The results showed that the highest pharmaceutical concentrations in untreated water were caffeine, ibuprofen, and acetaminophen, at concentrations of 224, 77.2, and 70 ng/L, respectively. Concentrations of pharmaceuticals were generally higher during the winter months, as compared to those in the summer due, presumably, to smaller water quantities in the winter, even though pharmaceutical loadings into the receiving waters were similar for both seasons."

http://www.ncbi.nlm.nih.gov/pubmed/21185051

Reviews In Environmental Contamination And Toxicology • July 2010

Chemicals of emerging concern in the Great Lakes Basin: an analysis of environmental exposures

Author information

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Abstract

This review and statistical analysis was conducted to better understand the nature and significance of environmental exposures in the Great Lakes Basin and watershed to a variety of environmental contaminants. These contaminants of interest included current-use pesticides, pharmaceuticals, organic wastewater contaminants, alkylphenol ethoxylates, perfluorinated surfactants, flame retardants, and chlorinated paraffins. The available literature was critically reviewed and used to develop a database containing 19,611 residue values for 326 substances. In many papers, sampling locations were characterized as being downstream from municipal wastewater discharges, receiving waters for industrial facilities, areas susceptible to agricultural or urban contamination, or harbors and ports. To develop an initial assessment of their potential ecological significance, the contamination levels found were compared with currently available regulatory standards, guidelines, or criteria. This review was prepared for the IJC multi-board work group, and served as background material for an expert consultation, held in March, 2009, in which the significance of the contaminants found was discussed. Moreover, the consultation attempted to identify and assess opportunities for strengthening future actions that will protect the Great Lakes. Based on the findings and conclusions of the expert consultation, it is apparent that a wide variety of chemicals of emerging concern have been detected in environmental media (air, water, sediment, biota) from the Great Lakes Basin, although many are present at only trace levels. Although the presence of these contaminants raises concerns in the public and among the scientific community, the findings must be placed in context. Significant scientific interpretation is required to understand the extent to which these chemicals may pose a threat to the ecosystem and to human health. The ability to detect chemicals in environmental media greatly surpasses our ability to understand the implications of such findings. As advances in analytical technologies occur, it is probable that substances previously found to be non-detectable will be detected. However, their presence in environmental media should not be construed to mean that they are necessarily toxic or hazardous. Current-use pesticides are tightly regulated and extensive efforts have been made to analyze for their presence in surface waters from the Great Lakes Basin. The concentrations found in surface waters for many of the pesticides are below current regulatory criteria. However, the concentrations of certain pesticides exceeded current criteria in 6-32% of the samples analyzed. Detectable concentrations of pharmaceutical compounds were present in 34% of the surface water samples. Various prescription and non-prescription drugs were detected, most frequently at locations that were proximate to the point of discharge from wastewater treatment plants or agricultural operations. At present, there are no standards, guidelines, or criteria with which to compare these contaminant concentrations. Concentrations of alkylphenol ethoxylates and their metabolites have been well studied. All surface water nonylphenol concentrations were below US ambient water quality criteria. However, the concentrations reported for some locations exceeded Canadian guidelines for water or sediment. Only limited data were available for a wide variety of organic wastewater contaminants. Measured concentrations in Great Lakes waters were generally low. Where criteria exist for comparison, the concentrations found were generally below the associated regulatory standards. However, exceedences were noted for some classes of compounds, including phthalates and polycyclic aromatic hydrocarbons. The highest environmental concentrations were reported in biota for a number of persistent, bioaccumulative, and toxic compounds (e.g., polybrominated diphenyl ethers, perfluorinated surfactants). Various stewardship as well as government risk assessment and risk management programs have been implemented over the past years for many of these compounds. Because risk management strategies for some of these contaminants have been implemented only recently, their impact on environmental concentrations, to date, remains unclear. Current evidence suggests that the concentrations of some brominated flame retardants are trending downward, while the concentrations of others appear to be increasing. Regulatory criteria are not available for many of the chemicals of emerging concern that were detected in the Great Lakes Basin. When criteria do exist, it is important to recognize that they were developed based on the best available science at the time. As the science evolves, regulatory criteria must be reassessed in light of new findings (e.g., consideration of new endpoints and mechanisms of action). Further, there are significant scientific gaps in our ability to interpret environmental monitoring data, including the need for: (a) improving the understanding of the effects of mixtures, (b) information on use of, and the commercial life cycle of chemicals and products that contain them, (c) information on source contributions and exposure pathways, and (d) the need for thoughtful additional regulatory,environmental, and health criteria. Discharges from wastewater treatment plants were identified as an important source of contaminants to surface waters in the Great Lakes Basin. Combined sewer overflows and agricultural operations were also found to be important contributors to concentrations in surface waters. Concentrations of many of the chemicals were generally the highest in the vicinity of these sources, decline with increasing distance from sources, and were generally low or non-detectable in the open waters of the Great Lakes.

http://www.ncbi.nlm.nih.gov/pubmed/20652664

Reviews In Environmental Contamination And Toxicology • January 2009

Assessing the discharge of pharmaceuticals along the Dutch coast of the North Sea

Author information

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Abstract

“This chapter assessed the annual median discharge of over 100 pharmaceuticals to the DCZ. Calculations were based on pharmaceutical concentrations in surface-, sewage-, and industrial water in the Netherlands. In 2002, riverine discharge to the DCZ for individual pharmaceuticals varied from 0 (concentration below LOD) to 27 t yr(-1). However, in 2002 the annual amount was less than 2 t for 75% of the studied pharmaceuticals. The highest loads were calculated for X-ray contrast media, that is, values of 18-27 t yr(-1) for iopromide. The top 20 pharmaceuticals discharged by rivers to the DCZ are dominated by X-ray contrast media (n = 7), followed by antibiotics (n = 6), analgesics/antipyretics/anti-inflammatory drugs (n = 2), beta blockers (n = 2), fibrates/lipid regulators (n = 1), veterinary antibiotics (n = 1), and others (n = 1). The direct discharge (sewage water and industrial water) of pharmaceuticals to the DCZ, in 2002, for individual pharmaceuticals varied from < 0.0009 to 0.27 t yr(-1) for sewage water, and from < 0.0009 to 0.33 t yr(-1) for industrial wastewater. The highest loads were calculated for sotalol (beta blocker) and diatrizoic acid (X-ray contrast medium) in sewage water and industrial wastewater, respectively. The direct discharge of pharmaceuticals to the DCZ is < 5% of that from riverine discharge. The discharge of these pharmaceuticals to the DCZ in 2002 is in the same order of magnitude as the discharge rates of the mandatory OSPAR substances Cd (8.8-10 t yr(-1)) and Hg (3.3 t yr(-1)), and are higher than the discharge rates of the mandatory substance lindane (0.041-0.055 t yr(-1)) and the recommended substance PCBs (0.217 t yr(-1)). Although some pharmaceuticals are discharged in significant amounts to the DCZ, the human and ecotoxicological risks of these highly biologically active compounds are largely unknown. To determine the environmental hazard and risk of discharged pharmaceuticals to the marine environment, future research should focus on a baseline study and a risk assessment of the discharged pharmaceuticals in the DCZ.”

http://www.ncbi.nlm.nih.gov/pubmed/19110938

“... the levels of many emerging Disinfection By-Products are increased by alternative disinfectants (primarily ozone or chloramines) compared to chlorination, and many emerging Disinfection By-Products are more genotoxic than some of the regulated Disinfection By-Products.”

Mutation Research • November 2007

Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-productsin drinking water: a review and roadmap for research

Author information

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Abstract

Disinfection by-products (DBPs) are formed when disinfectants (chlorine, ozone, chlorine dioxide, or chloramines) react with naturally occurring organic matter, anthropogenic contaminants, bromide, and iodide during the production of drinking water. Here we review 30 years of research on the occurrence, genotoxicity, and carcinogenicity of 85 DBPs, 11 of which are currently regulated by the U.S., and 74 of which are considered emerging DBPs due to their moderate occurrence levels and/or toxicological properties. These 74 include halonitromethanes, iodo-acids and other unregulated halo-acids, iodo-trihalomethanes (THMs), and other unregulated halomethanes, halofuranones (MX [3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone] and brominated MX DBPs), haloamides, haloacetonitriles, tribromopyrrole, aldehydes, and N-nitrosodimethylamine (NDMA) and other nitrosamines. Alternative disinfection practices result in drinking water from which extracted organic material is less mutagenic than extracts of chlorinated water. However, the levels of many emerging DBPs are increased by alternative disinfectants (primarily ozone or chloramines) compared to chlorination, and many emerging DBPs are more genotoxic than some of the regulated DBPs. Our analysis identified three categories of DBPs of particular interest. Category 1 contains eight DBPs with some or all of the toxicologic characteristics of human carcinogens: four regulated (bromodichloromethane, dichloroacetic acid, dibromoacetic acid, and bromate) and four unregulated DBPs (formaldehyde, acetaldehyde, MX, and NDMA). Categories 2 and 3 contain 43 emerging DBPs that are present at moderate levels (sub- to low-mug/L): category 2 contains 29 of these that are genotoxic (including chloral hydrate and chloroacetaldehyde, which are also a rodent carcinogens); category 3 contains the remaining 14 for which little or no toxicological data are available. In general, the brominated DBPs are both more genotoxic and carcinogenic than are chlorinated compounds, and iodinated DBPs were the most genotoxic of all but have not been tested for carcinogenicity. There were toxicological data gaps for even some of the 11 regulated DBPs, as well as for most of the 74 emerging DBPs. A systematic assessment of DBPs for genotoxicity has been performed for approximately 60 DBPs for DNA damage in mammalian cells and 16 for mutagenicity in Salmonella. A recent epidemiologic study found that much of the risk for bladder cancer associated with drinking water was associated with three factors: THM levels, showering/bathing/swimming (i.e., dermal/inhalation exposure), and genotype (having the GSTT1-1 gene). This finding, along with mechanistic studies, highlights the emerging importance of dermal/inhalation exposure to the THMs, or possibly other DBPs, and the role of genotype for risk for drinking-water-associated bladder cancer. More than 50% of the total organic halogen (TOX) formed by chlorination and more than 50% of the assimilable organic carbon (AOC) formed by ozonation has not been identified chemically. The potential interactions among the 600 identified DBPs in the complex mixture of drinking water to which we are exposed by various routes is not reflected in any of the toxicology studies of individual DBPs. The categories of DBPs described here, the identified data gaps, and the emerging role of dermal/inhalation exposure provide guidance for drinking water and public health research.

http://www.ncbi.nlm.nih.gov/pubmed/17980649

“Treatment with 4 individual [water] disinfection by-products as well as a mixture of them, caused the development of Aberrant crypt foci, the putative preneoplastic lesion of colon cancer.”

Toxicologic Pathology • December 2003

Induction of Transitional Cell Hyperplasia in the Urinary Bladder and Aberrant Crypt Foci in the Colon of Rats Treated with Individual and a Mixture of DrinkingWater Disinfection By-Products

Author Information

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Abstract

Cancer of the urinary bladder and colon are significant human health concerns. Epidemiological studies have suggested a correlation between these cancers and the chronic consumption of chlorinated surface water containing disinfection by-products (DBPs). The present study was designed to determine if exposure to DBPs would cause preneoplastic or neoplastic lesions in the urinary bladder and colon of rats, and what effect a mixture of DBPs would have on these lesions. Male and female Eker rats were treated via drinking water with low and high concentrations of potassium bromate, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), chloroform, or bromodichloromethane individually or in a mixture for 10 months. The urinary bladders and colons were examined for the presence of preneoplastic lesions. Cell proliferation in the urothelium was examined using immunohistochemical staining for bromodeoxyuridine. Aberrant crypt foci (ACF), as well as the number of individual crypts in each ACF, were identified and counted microscopically after staining with 0.2% methylene blue. Colon crypt cell proliferation and mitotic index were determined using immunohistochemical staining for proliferating cell nuclear antigen. Labeling indexes for the urinary bladder and colon were calculated based on the percentage of positively labeled cells. Treatment with the high dose of MX caused transitional epithelial hyperplasia and cell proliferation in the rat urinary bladder, and this effect was diminished in the high dose mixture animals. Treatment with 4 individual DBPs, as well as a mixture of them, caused the development of ACF, the putative preneoplastic lesion of colon cancer.

http://www.ncbi.nlm.nih.gov/pubmed/17980649

CHAPTER THIRTY-SIX

Energy Drinks

The Peer Review

Energy Drinks are dangerous, especially so by today's consumption standards, which for many users are, and especially for our youth, a daily or frequent purchase. Not only do they contain an unhealthy dose of caffeine, far more than most other dosage platforms, and not only are they absorbed rapidly for a physically recognizable, heart muscle defying jolt, they contain a wide variety of additional chemicals, preservatives, colors and dyes, artificial sweeteners and unhealthy sugars, emulsifiers and other poisonous additives that with any regular consumption at all, will kill you. The peer review on the ingredients in these drinks is clear and concise. The slick and expensive marketing campaigns promoted by greedy manufacturers of products known and proven to be harmful and sold with smug impunity are wholly irresponsible. Don't fall for the propaganda and the hype. Get your energy from wholesome whole foods, organic when possible. If we don't keep buying garbage like energy drinks the manufacturers will be forced to stop making garbage like energy drinks.

“Significant racial and ethnic differences exist in the dietary practices of California children. Increased fruit and vegetable consumption appears to be associated with parent education but not income.”

Journal Of The Academy Of Nutritionists And Dieticians • March 2016

Racial and Ethnic Disparities in Dietary Intake among California Children

Guerrero AD, Chung PJ.

Abstract

BACKGROUND

The prevalence of childhood obesity among racial and ethnic minority groups is high. Multiple factors affect the development of childhood obesity, including dietary practices.

OBJECTIVE

To examine the racial and ethnic differences in reported dietary practices among the largest minority groups of California children.

METHODS

Data from the 2007 and 2009 California Health Interview Survey were analyzed using multivariate regression with survey weights to examine how race, ethnicity, sociodemographic characteristics, and child factors were associated with specific dietary practices.

RESULTS

The sample included 15,902 children aged 2 to 11 years. In multivariate regressions, substantial differences in fruit juice, fruit, vegetable, sugar-sweetened beverages, sweets, and fast-food consumption were found among the major racial and ethnic groups of children. Asians regardless of interview language were more likely than whites to have low vegetable intake consumption (Asians English interview odds ratio [OR] 1.20, 95% CI 1.01 to 1.43; Asians non-English-interview OR 2.09, 95% CI 1.23 to 3.57) and low fruit consumption (Asians English interview OR 1.69, 95% CI 1.41 to 2.03; Asians non-English interview OR 3.04, 95% CI 2.00 to 4.6). Latinos regardless of interview language were also more likely than whites to have high fruit juice (Latinos English interview OR 1.54, 95% CI 1.28 to 1.84 and Latinos non-English interview OR 1.29, 95% CI 1.02 to 1.62) and fast-food consumption (Latinos English interview OR 1.74, 95% CI 1.46 to 2.08 and Latinos non-English interview OR 1.48, 95% CI 1.16 to 1.91); but Latinos were less likely than whites to consume sweets (Latinos English interview OR 0.81, 95% CI 0.66 to 0.99 and Latinos non-English interview OR 0.56, 95% CI 1.16 to 1.91).

CONCLUSIONS

Significant racial and ethnic differences exist in the dietary practices of California children. Increased fruit and vegetable consumption appears to be associated with parent education but not income. Our findings suggest that anticipatory guidance and dietary counseling might benefit from tailoring to specific ethnic groups to potentially address disparities in overweight and obesity.

http://www.ncbi.nlm.nih.gov/pubmed/26433453

“This study extends findings that energy drink use is associated with risk behavior, and it is the first study to show that energy drink use is associated with monetary delay discounting.”

Journal Of Caffeine Research • March 2016

Weekly Energy Drink Use Is Positively Associated with Delay Discounting and Risk Behavior in a Nationwide Sample of Young Adults

Author information

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Abstract

Background: Energy drink use is associated with increased risk behavior among adolescents and college students. This study examined this relationship in a nationwide sample of young adults and also examined relations between energy drink use and delay discounting. Methods: Participants were 874 U.S. adults 18-28 years of age with past 30-day consumption of caffeine and alcohol. Participants completed an online survey of energy drink use, drug use, sexual activity, alcohol misuse (alcohol use disorders identification test [AUDIT]), sensation seeking (four-item Brief Sensation Seeking Scale [BSSS-4]), and delay discounting of monetary rewards and condom use. Results: Over one-third of participants ($n=303$) reported consuming energy drinks at least once per week. Weekly energy drink users were more likely than less-than-weekly energy drink users to report a recent history of risk behaviors, including cigarette smoking (56% vs. 28%, $p<0.0001$), illicit stimulant use (22% vs. 6%, $p<0.0001$), and unprotected sex (63% vs. 45%, $p<0.0001$). Covariate-adjusted analyses found that weekly energy drink users did not have significantly higher BSSS-4 scores (3.5 vs. 3.1, $p=0.098$), but they had higher mean AUDIT scores (8.0 vs. 4.8, $p<0.0001$), and they more steeply discounted delayed monetary rewards. Although weekly energy drink users did not show steeper discounting of delayed condom use, they showed a lower likelihood of using a condom when one was immediately available. Conclusions: This study extends findings that energy drink use is associated with risk behavior, and it is the first study to show that energy drink use is associated with monetary delay discounting.

http://www.ncbi.nlm.nih.gov/pubmed/26989563

Advances In Nutrition • January 2015

Can energy drinks increase the desire for more alcohol?

By CA Marczinski CA

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Abstract

"Energy drinks, the fastest growing segment in the beverage market, have become popular mixers with alcohol. The emerging research examining the use of alcohol mixed with energy drinks (AmEDs) indicates that the combination of caffeine-containing energy drinks with alcohol may be riskier than the use of alcohol alone. The public health concerns arising from AmED use are documented in different research domains. Epidemiologic studies reveal that the consumption of AmEDs is frequent among young and underage drinkers, demographic groups that are more likely to experience the harms and hazards associated with alcohol use. In addition, for all consumers, elevated rates of binge drinking and risk of alcohol dependence have been associated with AmED use when compared to alcohol alone. Results from laboratory studies help explain why AmED use is associated with excessive intake of alcohol. When an energy drink (or caffeine) is combined with alcohol, the desire (or urge) to drink more alcohol is more pronounced in both humans and animals than with the same dose of alcohol alone. The experience of drinking alcohol appears to be more rewarding when combined with energy drinks. Given that caffeine in other foods and beverages increases preference for those products, further research on AmEDs may elucidate the underlying mechanisms that contribute to alcohol dependence."

http://www.ncbi.nlm.nih.gov/pubmed/25593148

Case Reports In Emergency Medicine • February 2015

STEMI Associated with Overuse of Energy Drinks

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Abstract

“Coronary artery disease (CAD) and ST-elevation myocardial infarction (STEMI) are predominantly diseases of middle-aged and older adults and when found in younger adults are usually associated with a strong family history. However, this report details the case of a nonobese 26-year-old Hispanic male who presented with an acute STEMI despite having no family history or other apparent risk factors for CAD or STEMI beyond a two pack-year smoking history and excessive energy drink consumption. The patient reported consuming between eight and ten 473 mL cans per day. Cardiac catheterization subsequently confirmed total occlusion of his left circumflex coronary artery.”

Full text, 2 Electrocardiograms and 10 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4350866/

“Nearly one in five students (18.2%) reported consuming energy drinks in a usual week. Use of energy drinks mixed with alcohol in the previous 12 months was reported by 17.3% of the sample, and was associated with race, spending money, and more frequent binge drinking.”

Canadian Journal Of Public Health • March 2015

Use of caffeinated energy drinks among secondary school students in Ontario: Prevalence and correlates of using energy drinks and mixing with alcohol

Author information

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Abstract

OBJECTIVES

Caffeinated energy drinks have become increasingly popular among young people, raising concern about possible adverse effects, including increased alcohol consumption and related risk behaviours. The current study examined consumption of caffeinated energy drinks and use of energy drinks with alcohol, as well as associations with socio-demographic and behavioural characteristics, among a sample of secondary school students in Ontario.

METHODS

Survey data from 23,610 grade 9-12 students at 43 purposefully sampled Ontario secondary schools participating in the baseline wave (2012/13) of the COMPASS study were analyzed using generalized linear mixed-effects models. Outcomes were any energy drink use, frequency of use, and use of alcohol mixed with energy drinks; covariates were age, sex, race, spending money, bodymass index (BMI), weight-related efforts and alcohol use. Two-way interactions between sex and other covariates were tested.

RESULTS

Nearly one in five students (18.2%) reported consuming energy drinks in a usual week. Use of energy drinks was associated (p < 0.01) with all socio-demographic variables examined and was more common among students who were male, off-reserve Aboriginal, had some spending money, had a BMI outside of “healthy” range, were trying to lose weight, and/or reported a higher intensity of alcohol use. Interactions with sex were observed for age, spending money and weight-related efforts. Use of energy drinks mixed with alcohol in the previous 12 months was reported by 17.3% of the sample, and was associated with race, spending money, and more frequent binge drinking.

CONCLUSION

Regular use of energy drinks was common among this sample of students and strongly linked to alcohol consumption.

http://www.ncbi.nlm.nih.gov/pubmed/26125234

“Energy drink manufacturers primarily advertise on channels that likely appeal to adolescents.”

Journal Of Nutritional And Educational Behavior • March 2015

Patterns of energy drink advertising over US television networks

Author information
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Abstract

OBJECTIVE
To describe programming themes and the inclusion of adolescents in the base audience for television channels with high levels of energy drink advertising airtime.
DESIGN
Secondary analysis of energy drink advertising airtime over US network and cable television channels (n = 139) from March, 2012 to February, 2013. Programming themes and the inclusion of adolescents in each channel's base audience were extracted from cable television trade reports.
MAIN OUTCOME MEASURE
Energy drink advertising airtime.
ANALYSIS
Channels were ranked by airtime; programming themes and the inclusion of adolescents in the base audience were summarized for the 10 channels with the most airtime.
RESULTS
Over the study year, 36,501 minutes (608 hours) were devoted to energy drink advertisements; the top 10 channels accounted for 46.5% of such airtime. Programming themes for the top 10 channels were music (n = 3), sports (n = 3), action-adventure lifestyle (n = 2), African American lifestyle (n = 1), and comedy (n = 1). MTV2 ranked first in airtime devoted to energy drink advertisements. Six of the 10 channels with the most airtime included adolescents aged 12-17 years in their base audience.
CONCLUSIONS AND IMPLICATIONS
Energy drink manufacturers primarily advertise on channels that likely appeal to adolescents. Nutritionists may wish to consider energy drink media literacy when advising adolescents about energy drink consumption.

http://www.ncbi.nlm.nih.gov/pubmed/25754297

“These findings suggest that many youth may be unaware or misinformed about the potential health effects and nutritional content of energy drinks.”

American Journal Of Health Promotion • March 2015

Perceptions about energy drinks are associated with energy drink intake among U.S. youth

Kumar G, Park S, Onufrak S.

Abstract

PURPOSE:
Energy drinks are growing in popularity among youth because of their stimulant properties. However, they can increase blood pressure and are associated with serious consequences such as cardiac arrest. This study examined the associations between energy drink perceptions and energy drink consumption among youth.

DESIGN:
The design was a cross-sectional study using the YouthStyles Survey 2011.

SETTING:
The online survey was administered at home.

SUBJECTS:
Subjects were youths aged 12 to 17 years in the summer of 2011 (n = 779).

MEASURES:
Energy drink consumption, perceptions about energy drinks, and sociodemographic and behavioral variables were measured.

ANALYSIS:
Chi-square and multivariable logistic regression analyses were used.

RESULTS:
Overall, 9% of youth drank energy drinks, 19.5% agreed that energy drinks are safe drinks for teens, and 12.5% agreed that energy drinks are a type of sports drink. The proportion of youth consuming energy drinks once per week or more was highest among youth aged 16 to 17 years and among those who are physically active three to six times a week. The odds for drinking energy drinks once per week or more was higher among youth who agreed that energy drinks are safe drinks for teens (odds ratios [OR] = 7.7, 95% confidence intervals [CI] =3.6, 16.4) and among those who agreed that energy drinks are a type of sports drink (OR = 5.0, 95% CI = 2.4, 10.7).

CONCLUSIONS:
These findings suggest that many youth may be unaware or misinformed about the potential health effects and nutritional content of energy drinks. Efforts to improve education among youth about the potential adverse effects of consuming energy drinks are needed.

http://www.ncbi.nlm.nih.gov/pubmed/24460002

“Emergency department visits due to energy drinks rose drastically from 2007 to 2011. Multinomial logistic regression indicated that men, those who had sex after substance use, those who had used drugs, and those with higher alcohol severity were more likely to be Combined users than Non-Users. Those with higher alcohol severity were also more likely to be Combined users than Separate users. Combining energy drinks and alcohol is associated with higher rates of other risk behaviors among young drinkers.”

Addiction Behavior • April 2015

Alcohol and energy drink use among adolescents seeking emergency department care

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Abstract

Emergency department (ED) visits due to energy drinks rose drastically from 2007 to 2011. Consuming alcohol mixed with energy drinks by young people is particularly concerning. Among youth (aged 14-20 years) in the ED reporting past-year alcohol use, we assessed frequency, reasons, and medical consequences of consuming alcohol and energy drinks in the same beverage or on the same occasion, and relationships with other risk behaviors. The sample included 439 youth (M(age)=18.6 years, SD=1.4; 41% male; 73% Caucasian): those who drank alcohol, but not energy drinks (Non-Users; 41%, n=178), those who drank alcohol and energy drinks on separate occasions (Separate; 23%, n=103), and those who combined alcohol and energy drinks in the same beverage or on the same occasion (Combined; 36%, n=158). Common reasons for combining energy drinks and alcohol were hiding the flavor of alcohol (39%) and liking the taste (36%). Common consequences were feeling jittery (71%) and trouble sleeping (46%). Combined users had the highest rates of risk behaviors (e.g., drug use, sexual risk behaviors, driving after drinking) and alcohol use severity. Multinomial logistic regression indicated that men, those who had sex after substance use, those who had used drugs, and those with higher alcohol severity were more likely to be Combined users than Non-Users. Those with higher alcohol severity were also more likely to be Combined users than Separate users. Combining energy drinks and alcohol is associated with higher rates of other risk behaviors among young drinkers. Future studies are needed to determine longitudinal relationships of energy drink use on substance use problem trajectories.

Full text, graphs, charts and 66 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4305014/

“Energy drink consumption is a health issue primarily of the adolescent and young adult male population. It is linked to increased substance abuse and risk-taking behaviors. The most common adverse events affect the cardiovascular and neurological systems. The most common ingredient in energy drinks is caffeine, and it is believed that the adverse events are related to its effects, as well as potentiating effects of other stimulants in these drinks.”

Postgraduate Medicine • April 2015

Energy drinks and their adverse health effects: A systematic review of the current evidence

Author information

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Abstract

PURPOSE

With the rising consumption of so-called energy drinks over the last few years, there has been a growing body of literature describing significant adverse health events after the ingestion of these beverages. To gain further insight about the clinical spectrum of these adverse events, we conducted a literature review.

METHODS

Using PubMed and Google-Scholar, we searched the literature from January 1980 through May 2014 for articles on the adverse health effects of energy drinks. A total of 2097 publications were found. We then excluded molecular and industry-related studies, popular media reports, and case reports of isolated caffeine toxicity, yielding 43 reports.

CONCLUSION

Energy drink consumption is a health issue primarily of the adolescent and young adult male population. It is linked to increased substance abuse and risk-taking behaviors. The most common adverse events affect the cardiovascular and neurological systems. The most common ingredient in energy drinks is caffeine, and it is believed that the adverse events are related to its effects, as well as potentiating effects of other stimulants in these drinks. Education, regulation, and further studies are required.

http://www.ncbi.nlm.nih.gov/pubmed/25560302

Use of Energy Drinks is ...

“associated with high rates of adverse effects and occurs in potentially dangerous situations like during exercise and with alcohol.”

Journal Of Epidemiology And Global Health • June 2015

Energy drink usage among university students in a Caribbean country: Patterns of use and adverse effects

Author information

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Abstract

OBJECTIVE

There has been little inquiry addressing whether or not concerns about adverse effects of energy drink usage are relevant in the Caribbean. This survey investigated energy drink usage and adverse consequences among tertiary level students in Trinidad and Tobago.

METHODS

A cross-sectional survey of 1994 students from eight institutions was conducted using a de novo questionnaire based on findings from a focus group of students. Chi-squared analyses and logistic regression were used to assess relationships between energy drink usage, adverse effects and other factors affecting energy drink use, and to verify predictors of energy drink use.

RESULTS

Prevalence of use was 86%; 38% were current users. Males were more likely to use, used more frequently and at an earlier age. Energy drinks were used most commonly to increase energy (50%), combat sleepiness (45%) and enhance academic performance (40%), and occurred during sports (23%) and mixed with alcohol (22.2%). The majority (79.6%) consumed one energy drink per sitting; 62.2% experienced adverse effects, most commonly restlessness (22%), jolt and crash (17.1%) and tachycardia (16.6%). Awareness of adverse effects was associated with no use (p=0.004), but adverse effects were not a deterrent to continued use.

CONCLUSION

Energy drink usage is prevalent among students. The use is not excessive, but associated with high rates of adverse effects and occurs in potentially dangerous situations like during exercise and with alcohol. There is a need to educate students about the potential adverse effects of energy drinks.

Full text, graphs, sample questionnaire and 38 references

http://www.sciencedirect.com/science/article/pii/S2210600614000525

“These products pose a risk of caffeine toxicity when consumed by some young people, and there is evidence of other troubling physiological and behavioral effects associated with their consumption by youth.”

Nutrition Review • July 2015

Energy drinks and adolescents: what’s the harm?

Author information

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Abstract

Concerns about potential dangers from energy drink consumption by youth have been raised by health experts, whereas energy drink manufacturers claim these products are safe and suitable for marketing to teens. This review summarizes the evidence used to support both sides of the debate. Unlike most beverage categories, sales of energy drinks and other highly caffeinated products continue to grow, and marketing is often targeted to youth under the age of 18 years. These products pose a risk of caffeine toxicity when consumed by some young people, and there is evidence of other troubling physiological and behavioral effects associated with their consumption by youth. The US Food and Drug Administration has indicated it will reexamine the safety of caffeine in the food supply; however, more research is needed to better understand youth consumption of energy drinks and caffeine in general, as well as the long-term effects on health. Meanwhile, policymakers and physician groups have called on energy drink manufacturers to take voluntary action to reduce the potential harm of their products, including placing restrictions on marketing to youth under the age of 18 years. Additional regulatory and legislative options are also being discussed.

http://www.ncbi.nlm.nih.gov/pubmed/26024547

Journal Of Studies On Alcohol And Drugs • July 2015

Combined Use of Alcohol and Energy Drinks Increases Participation in High-Risk Drinking and Driving Behaviors Among College Students

Author information

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> “Combined use of alcohol and energy drinks may place drinkers at greater risk when compared with those who consume only alcohol. College students in this sample who combined alcohol and energy drinks were more likely to participate in high-risk driving behaviors than those who consumed only alcohol.”

Abstract

OBJECTIVE

A recent study suggested that college students who combined alcohol and energy drinks were more likely than students who consumed only alcohol to drive when their blood alcohol concentration (BAC) was higher than the .08% limit and to choose to drive despite knowing they had too much alcohol to drive safely. This study sought to replicate those findings with a larger sample while also exploring additional variables related to impaired driving.

METHOD

College students (N = 549) completed an anonymous online survey to assess differences in drinking and driving-related behaviors between alcohol-only users (n = 281) and combined alcohol-energy drink users (n = 268).

RESULTS

Combined users were more likely than alcohol-only users to choose to (a) drive when they perceived they were over the .08% BAC limit (35.0% vs. 18.1%, $p < .001$), (b) drive despite knowing they had too much alcohol to drive safely (36.3% vs. 17.0%, $p < .001$), and (c) be a passenger when they knew the driver had too much alcohol to drive safely (44.1% vs. 23.6%, $p < .001$). Combined users were significantly more likely ($p < .001$) to report indicators of high-risk alcohol use, such as larger number of drinks consumed, number of days drinking, number of days drunk, number of heavy episodic drinking episodes, greatest number of drinks on one occasion, and average hours of consumption.

CONCLUSIONS

Combined use of alcohol and energy drinks may place drinkers at greater risk when compared with those who consume only alcohol. College students in this sample who combined alcohol and energy drinks were more likely to participate in high-risk driving behaviors than those who consumed only alcohol.

http://www.ncbi.nlm.nih.gov/pubmed/26098038

> “... traumatic brain injuries remains a disabling and common condition among adolescents and the consumption of alcohol, energy drinks, and alcohol mixed with energy drinks further increase the odds of traumatic brain injuries among adolescents.”

PLoS One • September 2015

Energy Drinks, Alcohol, Sports and Traumatic Brain Injuries among Adolescents

Author information

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Abstract

IMPORTANCE

The high prevalence of traumatic brain injuries (TBI) among adolescents has brought much focus to this area in recent years. Sports injuries have been identified as a main mechanism. Although energy drinks, including those mixed with alcohol, are often used by young athletes and other adolescents they have not been examined in relation to TBI.

OBJECTIVE

We report on the prevalence of adolescent TBI and its associations with energy drinks, alcohol and energy drink mixed in with alcohol consumption.

DESIGN, SETTINGS AND PARTICIPANTS

Data were derived from the Centre for Addiction and Mental Health’s 2013 Ontario Student Drug Use and Health Survey (OSDUHS). This population-based cross-sectional school survey included 10,272 7th to 12th graders (ages 11-20) who completed anonymous self-administered questionnaires in classrooms.

MAIN OUTCOME MEASURES

Mild to severe TBI were defined as those resulting in a loss of consciousness for at least five minutes, or being hospitalized for at least one night. Mechanism of TBI, prevalence estimates of TBI, and odds of energy drink consumption, alcohol use, and consumption of energy drinks mixed with alcohol are assessed.

RESULTS

Among all students, 22.4% (95% CI: 20.7, 24.1) reported a history of TBI. Sports injuries remain the main mechanism of a recent (past year) TBI (45.5%, 95% CI: 41.0, 50.1). Multinomial logistic regression showed that relative to adolescents who never sustained a TBI, the odds of sustaining a recent TBI were greater for those consuming alcohol, energy drinks, and energy drinks mixed in with alcohol than abstainers. Odds ratios were higher for these behaviors among students who sustained a recent TBI than those who sustained a former TBI (lifetime but not past 12 months). Relative to recent TBI due to other causes of injury, adolescents who sustained a recent TBI while playing sports had higher odds of recent energy drinks consumption than abstainers.

CONCLUSIONS AND RELEVANCE

TBI remains a disabling and common condition among adolescents and the consumption of alcohol, energy drinks, and alcohol mixed with energy drinks further increase the odds of TBI among adolescents. These associations warrant further investigation.

Full text, graphs, charts and 41 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4572704/

“... as results of this study suggest consumption of these beverages is associated with unhealthy dietary behaviours and a greater BMI.”

Perspectives In Public Health • November 2015

Energy drink consumption is associated with unhealthy dietary behaviours among college youth

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Abstract

AIM

Energy drink consumption has been associated with a variety of health risk behaviours, yet little research has explored the relationship between energy drinks and dietary behaviours of emerging adults. Therefore, the purpose of this study was to explore the relationship between energy drink consumption and dietary behaviours among energy drink users and non-users within a sample of college youth.

METHODS

College freshmen (n=585, m age=18.7 years; 47% non-Hispanic White, 20.9% Hispanic, 25.5% Asian, 2.7% non-Hispanic Black and 4.4% other; 56% female), at a large, southwest university self-reported their energy drink consumption in the past week and a variety of dietary behaviours, including past week soda, diet soda, pre-packaged salty snacks, pre-packaged sweet snacks, fast food, restaurant food, frozen food, fruits, vegetables, milk and breakfast consumption. Linear regression analyses were run to determine associations between energy drink consumption and dietary behaviour among users and non-users of energy drinks. Analyses controlled for gender, race/ethnicity and body mass index (BMI).

RESULTS

Overall, 17.5% of students had consumed energy drinks in the past week. Energy drink users were more likely to be male, White and have a greater BMI. Students also reported low past week intake of fruits, vegetables, milk and breakfast. Past week energy drink consumption was associated with increased soda and frozen meal consumption.

CONCLUSION

Given a rapidly expanding energy drink market, future dietary interventions among college youth may want to consider the implications of energy drinks, as results of this study suggest consumption of these beverages is associated with unhealthy dietary behaviours and a greater BMI.

http://www.ncbi.nlm.nih.gov/pubmed/25667166

“Energy drinks are associated with increased platelet activity via arachidonic acid-induced platelet aggregation within 1 h of consumption. Although larger clinical studies are needed to further address the safety and health concerns of these drinks, the increased platelet response may provide a mechanism by which energy drinks increase the risk of adverse cardiovascular events.”

Journal Of Surgery Research • December 2015

Hypercoagulability after energy drink consumption

Author information

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Abstract

BACKGROUND

Energy drink consumption in the United States has more than doubled over the last decade and has been implicated in cardiac arrhythmias, myocardial infarction, and even sudden cardiac death. We hypothesized that energy drink consumption may increase the risk of adverse cardiovascular events by increasing platelet aggregation, thereby resulting in a relatively hypercoagulable state and increased risk of thrombosis.

METHODS

Thirty-two healthy volunteers aged 18-40 y were given 16 oz of bottled water or a standardized, sugar-free energy drink on two separate occasions, 1-wk apart. Beverages were consumed after an overnight fast over a 30-min period. Coagulation parameters and platelet function were measured before and 60 min after consumption using thrombelastography and impedance aggregometry.

RESULTS

No statistically significant differences in coagulation were detected using kaolin or rapid thrombelastography. In addition, no differences in platelet aggregation were detected using ristocetin, collagen, thrombin receptor-activating peptide, or adenosine diphosphate-induced multiple impedance aggregometry. However, compared to water controls, energy drink consumption resulted in a significant increase in platelet aggregation via arachidonic acid-induced activation (area under the aggregation curve, 72.4 U versus 66.3 U; $P = 0.018$).

CONCLUSIONS

Energy drinks are associated with increased platelet activity via arachidonic acid-induced platelet aggregation within 1 h of consumption. Although larger clinical studies are needed to further address the safety and health concerns of these drinks, the increased platelet response may provide a mechanism by which energy drinks increase the risk of adverse cardiovascular events.

http://www.ncbi.nlm.nih.gov/pubmed/26188956

“About 1 in 9 youth reported receiving counseling discouraging Energy Drink consumption from their doctor/nurse, and a greater proportion of youth who were screened about Energy Drinks also reported Energy Drink consumption. Efforts by health care providers to educate youth about potential harms of consuming Energy Drinks are needed.”

Patient Education Counseling • February 2014

Association between reported screening and counseling about energy drinks and energy drink intake among U.S. adolescents

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Abstract

OBJECTIVE

Possible adverse health consequences of excessive energy drink (ED) consumption have led to recommendations by the American Academy of Pediatrics discouraging ED intake by youth. However, limited information on ED counseling by health care providers exists.

METHODS

Data was obtained from the 2011 YouthStyles Survey administered to youth aged 12-17 (n=815). The outcome variable was ED consumption (none vs. ≥1 time/week) and exposure variables were screening and counseling about ED (if doctor/nurse asked about ED consumption and if doctor/nurse recommended against ED consumption).

RESULTS

Approximately 8.5% of youth consumed energy drinks weekly, 11.5% reported being asked by their doctor/nurse about frequency of ED consumption, and 11.1% were advised by their doctor/nurse against ED intake. Multivariable logistic regression analysis revealed that the odds for drinking ED ≥1 time/week was significantly higher in youth who were asked how often they drank ED by their doctor/nurse (odds ratio=2.46) vs. those who were not asked.

CONCLUSION

About 1 in 9 youth reported receiving counseling discouraging ED consumption from their doctor/nurse, and a greater proportion of youth who were screened about ED also reported ED consumption.

PRACTICE IMPLICATIONS

Efforts by health care providers to educate youth about potential harms of consuming ED are needed.

http://www.ncbi.nlm.nih.gov/pubmed/24176609

Current Opinions In Psychiatry • July 2014

Review of the energy drink literature from 2013: findings continue to support most risk from mixing with alcohol

Author information

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Abstract

PURPOSE OF REVIEW

In the field of caffeine research, interest in and concern for energy drink consumption have grown. Most caffeine-related research studies published in 2013 focused on energy drink consumption. This article reviews this literature.

RECENT FINDINGS

Prevalence of energy drink consumption varies by measure and age group. Lack of a standardized definition of use inhibits comparison across studies. Studies reviewed show that energy drink consumption is generally low, but the minority who drink the most may be consuming at unsafe levels. Energy drinks are popular among adolescents and young adults. They boost energy and alertness in some conditions, but may have adverse hemodynamic effects. Harmful consequences, including involvement in risky driving, riding with an intoxicated driver and being taken advantage of sexually, were reported significantly more often by adolescents and young adults who combined energy drinks with alcohol compared with those who did not.

SUMMARY

This review of recent literature focused on prevalence, motivation, and consequences of energy drink use. Clear findings emerged only on the dangers of mixing alcohol and energy drinks. The lack of a standardized measure made the comparison across studies difficult. Future research should extend and clarify these findings using standardized measures of use.

http://www.ncbi.nlm.nih.gov/pubmed/24852059

“Combining energy drinks with alcohol increased the urge to drink alcohol relative to drinking alcohol alone.”

Alcoholism, Clinical And Experimental Research • August 2014

The effect of energy drinks on the urge to drink alcohol in young adults

Author information

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Abstract

BACKGROUND

Recently, Marczinski and colleagues (2013) showed that energy drinks combined with alcohol augment a person’s desire to drink more alcohol relative to drinking alcohol alone. The current study replicates the findings of Marczinski and colleagues (2013) using a robust measure of alcohol craving.

METHODS

Seventy-five participants aged 18 to 30 years were assigned to an alcohol only or alcohol+energy drink condition in a double-blind randomized pre- versus posttest experiment. Participants received a cocktail containing either 60 ml of vodka and a Red Bull(®) Silver Edition energy drink (alcohol+energy drink condition) or 60 ml of vodka with a soda water vehicle (alcohol-only condition); both cocktails contained 200 ml of fruit drink. The primary outcome measure was the Alcohol Urge Questionnaire taken at pretest and at 20 minutes (posttest). Other measures taken at posttest were the Biphasic Alcohol Effects Questionnaire, the Drug Effects Questionnaire, and breath alcohol concentration (BAC).

RESULTS

The alcohol+energy drink condition showed a greater pre- versus posttest increase in urge to drink alcohol compared with the alcohol-only condition ($B = 3.24$, $p = 0.021$, $d = 0.44$). Participants in the alcohol+energy drink condition had significantly higher ratings on liking the cocktail and wanting to drink more of the cocktail, and lower BACs, than the alcohol-only condition. When examined at specific BACs, the effect of the energy drink on the pre- to posttest increase in urge to drink was largest and only significant at BACs of 0.04-0.05 (cf. < 0.04 g/dl).There were no significant differences in stimulation, sedation, feeling the effects of the cocktail, or feeling high.

CONCLUSIONS

Combining energy drinks with alcohol increased the urge to drink alcohol relative to drinking alcohol alone. More research is needed to understand what factors mediate this effect and whether it increases subsequent alcohol consumption.

http://www.ncbi.nlm.nih.gov/pubmed/25041069

Nutrition Review • October 2014

Effect of energy drink and caffeinated beverage consumption on sleep, mood, and performance in children and adolescents

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Abstract

"The increasing availability of highly caffeinated beverages, including energy drinks, in the United States has resulted in a rise in consumption by children and adolescents. In addition, there is mounting evidence that these products are often consumed by youth for their perceived fatigue-mitigating and mood- or performance-enhancing effects. Although such perceptions by children and adolescents about the potential consequences of caffeine consumption are highly likely to influence decision making regarding the use of such products, there is still a relative paucity of studies that focus on the effect of caffeinated beverages on sleep, mood, and performance in the pediatric population. This review summarizes the following aspects of this topic, as derived from the information currently available: 1) the perception, among youth, of caffeine's risks and benefits and the sources of information about caffeine, particularly with regard to sleep, mood, and performance; 2) the bidirectional effect of caffeine on sleep in children and adolescents and the association of caffeine with other sleep-related practices, and 3) the evidence that supports caffeine as a performance and mood enhancer as well as a countermeasure to sleepiness in the pediatric population. Finally, gaps in knowledge are identified, and a direction for future research is outlined."

http://www.ncbi.nlm.nih.gov/pubmed/25293545

Nutrition Review • October 2014

Performance outcomes and unwanted side effects associated with energy drinks

Author information

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Abstract

"Energy drinks are increasingly popular among athletes and others. Advertising for these products typically features images conjuring great muscle power and endurance; however, the scientific literature provides sparse evidence for an ergogenic role of energy drinks. Although the composition of energy drinks varies, most contain caffeine; carbohydrates, amino acids, herbs, and vitamins are other typical ingredients. This report analyzes the effects of energy drink ingredients on prolonged submaximal (endurance) exercise as well as on short-term strength and power (neuromuscular performance). It also analyzes the effects of energy drink ingredients on the fluid and electrolyte deficit during prolonged exercise. In several studies, energy drinks have been found to improve endurance performance, although the effects could be attributable to the caffeine and/or carbohydrate content. In contrast, fewer studies find an ergogenic effect of energy drinks on muscle strength and power. The existing data suggest that the caffeine dose given in studies of energy drinks is insufficient to enhance neuromuscular performance. Finally, it is unclear if energy drinks are the optimal vehicle to deliver caffeine when high doses are needed to improve neuromuscular performance."

http://www.ncbi.nlm.nih.gov/pubmed/25293550

Nutrition Review • October 2014

Performance effects and metabolic consequences of caffeine and caffeinated energy drink consumption on glucose disposal

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Abstract

"This review documents two opposing effects of caffeine and caffeine-containing energy drinks, i.e., their positive effects on athletic performance and their negative impacts on glucose tolerance in the sedentary state. Analysis of studies examining caffeine administration prior to performance-based exercise showed caffeine improved completion time by 3.6%. Similar analyses following consumption of caffeine-containing energy drinks yielded positive, but more varied, benefits, which were likely due to the diverse nature of the studies performed, the highly variable composition of the beverages consumed, and the range of caffeine doses administered. Conversely, analyses of studies administering caffeine prior to either an oral glucose tolerance test or insulin clamp showed a decline in whole-body glucose disposal of ~30%. The consequences of this resistance are unknown, but there may be implications for the development of a number of chronic diseases. Both caffeine-induced performance enhancement and insulin resistance converge with the primary actions of caffeine on skeletal muscle."

http://www.ncbi.nlm.nih.gov/pubmed/25293551

Nutrition Reviews • October 2014

Energy drinks mixed with alcohol: what are the risks?

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Abstract

“Energy drinks are popular beverages that typically include high levels of caffeine and other ingredients such as taurine, or caffeine-containing herbs, such as guarana. While energy drinks are often consumed alone, they are also frequently used as mixers for alcoholic beverages. This review summarizes what is known about the scope of use of alcohol mixed with energy drinks, the risks associated with such mixtures, and the objective laboratory data examining how the effects of their consumption differ from consuming alcohol alone. The weight of the evidence reveals that consuming alcohol mixed with energy drinks is riskier than consuming alcohol alone and constitutes a public health concern. Consumption of these mixed beverages is frequent, especially in young and underage drinkers, and compared with alcohol alone, their use is associated with elevated rates of binge drinking, impaired driving, risky sexual behavior, and risk of alcohol dependence. Laboratory research (human and animal) has demonstrated that consuming alcohol mixed with energy drinks leads to altered subjective states including decreased perceived intoxication, enhanced stimulation, and increased desire to drink/increased drinking compared to consuming alcohol alone. Possible underlying mechanisms explaining these observations are highlighted in this review.”

http://www.ncbi.nlm.nih.gov/pubmed/25293549

“The ingestion of an energy drink with [just] 3 mg/kg of caffeine increased the prevalence of side effects. The presence of these side effects was similar between male and female participants.”

British Journal Of Nutrition • November 2014

The use of energy drinks in sport: perceived ergogenicity and side effects in male and female athletes

Author information

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Abstract

The use of caffeine containing energy drinks has dramatically increased in the last few years, especially in the sport context because of its reported ergogenic effect. The ingestion of low to moderate doses of caffeinated energy drinks has been associated with adverse side effects such as insomnia or increased nervousness. The aim of the present study was to assess psycho-physiological changes and the prevalence of side effects resulting from the ingestion of 3 mg caffeine/kg body mass in the form of an energy drink. In a double-blind and placebo controlled experimental design, ninety experienced and low-caffeine-consuming athletes (fifty-three male and thirty-seven female) in two different sessions were provided with an energy drink that contained 3 mg/kg of caffeine or the same decaffeinated energy drink (placebo; 0 mg/kg). At 60 min after the ingestion of the energy drink, participants completed a training session. The effects of ingestion of these beverages on psycho-physiological variables during exercise and the rate of adverse side effects were measured using questionnaires. The caffeinated energy drink increased self-perceived muscle power during exercise compared with the placebo beverage (6·41 (sd 1·7) v. 5·66 (sd 1·51); P= 0·001). Moreover, the energy drink produced a higher prevalence of side effects such as insomnia (31·2 v. 10·4 %; P< 0·001), nervousness (13·2 v. 0 %; P= 0·002) and activeness (16·9 v. 3·9 %; P= 0·007) than the placebo energy drink. There were no sex differences in the incidence of side effects (P>0·05). The ingestion of an energy drink with 3 mg/kg of caffeine increased the prevalence of side effects. The presence of these side effects was similar between male and female participants.

http://www.ncbi.nlm.nih.gov/pubmed/25212095

“Energy drinks are emerging as a public health threat.”

Journal Of Public Health Policy • May 2013

Energy drinks: an emerging public health hazard for youth

Author information

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Abstract

Energy drinks are emerging as a public health threat and are increasingly consumed by youth internationally. Energy drinks contain high levels of caffeine, sugar, and novel ingredients, and are often marketed through youth-oriented media and venues. We review these practices and the current inconsistent state of labeling. We also examine international support for regulation of these products, including a survey showing that 85 per cent of United States parents agreed that regulations requiring caffeine content disclosure and warning labels on energy drinks are warranted. We then examine the regulatory structure for energy drinks in the United States, analyzing legal and self-regulatory strategies to protect consumers, especially youth, from these potentially dangerous products. Recommended government interventions include revised labeling requirements, addressing problematic ingredients, and enacting retail restrictions. We conclude by identifying areas for future research.

http://www.ncbi.nlm.nih.gov/pubmed/23486464

“Caffeine, which is readily available to minors, is the most commonly used psychoactive substance in the world and imposes a potentially harmful influence on health, academic performance, and personal adjustments.”

Journal Of The American Academy Of Nurse Practitioners • February 2012

Energy drinks: what is all the hype?
The dangers of energy drink consumption

By M. Rath

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Abstract

PURPOSE

To describe the adverse effects associated with energy drink consumption among adolescents and young adults.

DATA SOURCES

Review of literature utilizing Medscape, the Internet, MD Consult, and CINAHL. The following search terms were used: Energy drinks, caffeine, guarana, taurine, ginseng, sugar, and caffeine toxicity. Search was limited to English language sources from 2005 to 2010.

CONCLUSIONS

The popularity of energy drinks and the rapid growth of their excessive consumption among adolescents and young adults have brought about great concern in regards to overall health and well-being. Caffeine, which is readily available to minors, is the most commonly used psychoactive substance in the world and imposes a potentially harmful influence on health, academic performance, and personal adjustments. Teens and young adults account for nearly $2.3 billion of energy drink sales. Adolescents and young adults are often unaware that various products, such as energy drinks, herbal medications, and various other medications that promote alertness, contain caffeine. When these products are taken together, caffeine toxicity and severe adverse effects can occur.

IMPLICATIONS FOR PRACTICE

Practitioners need to be aware of the consequences of energy drink consumption and be prepared to provide appropriate patient education.

http://www.ncbi.nlm.nih.gov/pubmed/22324861

“... energy drinks should be considered a novel exposure. The high doses of caffeine, often in combination with ingredients with unknown safety profiles, mandates urgent research on the safety of energy drink use in children and adolescents.”

Current Opinions In Pediatrics • April 2012

Toxicity of energy drinks

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Abstract

PURPOSE OF REVIEW

‘Energy drinks’, ‘energy shots’ and other energy products have exploded in popularity in the past several years; however, their use is not without risk. Caffeine is the main active ingredient in energy drinks, and excessive consumption may acutely cause caffeine intoxication, resulting in tachycardia, vomiting, cardiac arrhythmias, seizures, and death. The effects of chronic high-dose caffeine intake in children and adolescents are unknown. Caffeine may raise blood pressure, disrupt adolescent sleep patterns, exacerbate psychiatric disease, cause physiologic dependence, and increase the risk of subsequent addiction.

RECENT FINDINGS

Coingestion of caffeine and ethanol has been associated with increased risk-taking behaviors, harm to adolescent users, impaired driving, and increased use of other illicit substances. The toxicity of ingredients often present in energy drinks, such as taurine, niacin, and pyridoxine, is less well defined. Recent and significant literature describing adverse events associated with energy drink use are reviewed.

SUMMARY

Although prior studies have examined the effects of caffeine in adolescents, energy drinks should be considered a novel exposure. The high doses of caffeine, often in combination with ingredients with unknown safety profiles, mandates urgent research on the safety of energy drink use in children and adolescents. Regulation of pediatric energy drink use may be a necessary step once the health effects are further characterized.

http://www.ncbi.nlm.nih.gov/pubmed/22426157

Journal Of Psychopharmacology • November 2012

A case of acute suicidality following excessive caffeine intake

Author information

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Abstract

“Energy and stimulant drinks which contain caffeine provide enlivening effects, reduce fatigue and improve concentration and endurance. However, consumers may also experience physical and psychological side effects as a result of excessive consumption of caffeine within these drinks. Caffeine is known to exacerbate or induce some psychiatric conditions such as anxiety, panic attacks, psychosis and mania. Here we discuss a case of acute suicidality following sleep deprivation after the excessive consumption of a popular energy drink. We are concerned that such widely available stimulant drinks should contain health warnings or advice regarding moderating consumption.”

http://www.ncbi.nlm.nih.gov/pubmed/22472312

“Energy drinks have no therapeutic benefit, and many ingredients are understudied and not regulated. The known and unknown pharmacology of agents included in such drinks, combined with reports of toxicity, raises concern for potentially serious adverse effects in association with energy drink use.”

Pediatrics • March 2011

Health effects of energy drinks on children, adolescents, and young adults

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Abstract

OBJECTIVE

To review the effects, adverse consequences, and extent of energy drink consumption among children, adolescents, and young adults.

METHODS

We searched PubMed and Google using “energy drink,” “sports drink,” “guarana,” “caffeine,” “taurine,” “ADHD,” “diabetes,” “children,” “adolescents,” “insulin,” “eating disorders,” and “poison control center” to identify articles related to energy drinks. Manufacturer Web sites were reviewed for product information.

RESULTS

According to self-report surveys, energy drinks are consumed by 30% to 50% of adolescents and young adults. Frequently containing high and unregulated amounts of caffeine, these drinks have been reported in association with serious adverse effects, especially in children, adolescents, and young adults with seizures, diabetes, cardiac abnormalities, or mood and behavioral disorders or those who take certain medications. Of the 5448 US caffeine overdoses reported in 2007, 46% occurred in those younger than 19 years. Several countries and states have debated or restricted energy drink sales and advertising.

CONCLUSIONS

Energy drinks have no therapeutic benefit, and many ingredients are understudied and not regulated. The known and unknown pharmacology of agents included in such drinks, combined with reports of toxicity, raises concern for potentially serious adverse effects in association with energy drink use. In the short-term, pediatricians need to be aware of the possible effects of energy drinks in vulnerable populations and screen for consumption to educate families. Long-term research should aim to understand the effects in at-risk populations. Toxicity surveillance should be improved, and regulations of energy drink sales and consumption should be based on appropriate research.

Full text, graphs, charts and 121 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3065144/

“Energy drink consumption acutely increases platelet aggregation and decreases endothelial function in healthy young adults.”

American Journal Of Medicine • February 2010

Detrimental effects of energy drink consumption on platelet and endothelial function

Author information

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Abstract

BACKGROUND

Energy drink consumption has been anecdotally linked with sudden cardiac death and, more recently, myocardial infarction. As myocardial infarction is strongly associated with both platelet and endothelial dysfunction, we tested the hypothesis that energy drink consumption alters platelet and endothelial function.

METHODS

Fifty healthy volunteers (34 male, aged 22+/-2 years) participated in the study. Platelet aggregation and endothelial function were tested before, and 1 hour after, the consumption of 250 mL (1 can) of a sugar-free energy drink. Platelet function was assessed by adenosine diphosphate-induced (1 micromol/L) optical aggregometry in platelet-rich plasma. Endothelial function was assessed via changes in peripheral arterial tonometry and expressed as the reactive hyperemia index (RHI).

RESULTS

Compared with baseline values, there was a significant increase in platelet aggregation following energy drink consumption, while no change was observed with control (13.7+/-3.7% vs 0.3+/-0.8% aggregation, respectively, P <.01). Similarly, RHI decreased following energy drink consumption (-0.33+/-0.13 vs 0.07+/-0.12 RHI [control], P <.05). Mean arterial pressure significantly increased following energy drink consumption, compared with control (P <.05). Heart rate was unaffected by energy drink consumption.

CONCLUSION

Energy drink consumption acutely increases platelet aggregation and decreases endothelial function in healthy young adults.

http://www.ncbi.nlm.nih.gov/pubmed/20103032

“Other health concerns related to consumption of energy drinks include case reports of seizures and cardiac arrest following energy drink consumption and dental enamel erosion resulting from the acidity of energy drinks.”

Physicians Sportsmedicine • June 2010

Energy drinks: a review of use and safety for athletes

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Abstract

Energy drinks have increased in popularity in adolescents and young adults; however, concerns have been raised regarding the ingredients in energy drinks and their potential negative effects on health. Caffeine, the most physiologically active ingredient in energy drinks, is generally considered safe by the US Food and Drug Administration (FDA), although adverse effects can occur at varying amounts. Guarana, which contains caffeine in addition to small amounts of theobromine, theophylline, and tannins, is also recognized as safe by the FDA, although it may lead to caffeine toxicity when combined with caffeine. The amount of ginseng in energy drinks is typically far below the amount used as a dietary supplement, and is generally considered safe. Taurine, an intracellular amino acid, has been reported to have positive inotropic effects; however, this claim is not supported by research. Most energy drinks also contain sugar in an amount that exceeds the maximum recommended daily amount. Young athletes are increasingly using energy drinks because of the ergogenic effects of caffeine and the other ingredients found in these beverages. Energy drinks combined with alcohol are also gaining popularity in young adults, which poses significant concerns about health risks. Other health concerns related to consumption of energy drinks include case reports of seizures and cardiac arrest following energy drink consumption and dental enamel erosion resulting from the acidity of energy drinks.

http://www.ncbi.nlm.nih.gov/pubmed/20631477

Archives In Pediatrics • November 2010

Risks of energy drinks in youths

By AX Bigard
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Abstract

"The market value for energy drinks is continually growing and the annual worldwide energy drink consumption is increasing. However, issues related to energy drink ingredients and the potential for adverse health consequences remain to be elucidated. This aim of the present paper is to review the current knowledge on putative adverse effects of energy drinks, especially in youths. There are many energy drink brands in the worldwide market, even if only few brands are available in France. Although the energy drink content varies, these beverages often contain taurine, caffeine, vitamins B and carbohydrates. These drinks vary widely in both caffeine content (80 to 141 mg per can) and caffeine concentration. Except caffeine, the effects of energy drink ingredients on physical and cognitive performances remain controversial. Researchers identified moderate positive effects of energy drinks on performances, whereas others found contrary results. The adverse effects of energy drink can be related to either the toxicity of ingredients or specific situations in which energy drinks are used such as ingestion in combination with alcohol. Although the issue of taurine-induced toxic encephalopathy has been addressed, it is likely that the risk of taurine toxicity after energy drink consumption remains low. However, whether the prolonged use of energy drinks providing more than 3g taurine daily remains to be examined in the future. The consumption of energy drinks may increase the risk for caffeine overdose and toxicity in children and teenagers. The practice of consuming great amounts of energy drink with alcohol is considered by many teenagers and students a primary locus to socialize and to meet people. This pattern of energy drink consumption explains the enhanced risk of both caffeine and alcohol toxicity in youths. Twenty five to 40% of young people report consumption of energy drink with alcohol while partying. Consumption of energy drinks with alcohol during heavy episodic drinking is at risk of serious injury, sexual assault, drunk driving, and death. However, even after adjusting for alcohol consumption, students who consume alcohol mixed with energy drinks had dramatically higher rates of serious alcohol-related consequences. It has been reported that the subjective perceptions of some symptoms of alcohol intoxication are less intense after the combined ingestion of the alcohol plus energy drink; however, these effects are not detected in objective measures of motor coordination and visual reaction time."

http://www.ncbi.nlm.nih.gov/pubmed/20926266

CHAPTER THIRTY-SEVEN

Related Reports

The Peer Review

The reports and studies in this chapter are some of the most important reports included here. Don't sell them short because they're not categorized.

Gutting the Scientific Establishment: Australia's Business Model

By Dr. Binoy Kampmark

There is something so fundamentally wrong about equating the joy and genius of scientific discovery with profit and markets. Initial discoveries in quantum physics had nothing to do with the idea of pursuing a remorseless "bottom line" or some specious market concept. The results of such discoveries were, however, gargantuan. Eventually, applications arise, with various economic benefits. Patience, however, is a golden virtue in that regard.

Australia's scientific management (these comprise scientists who attempt to straddle the world of practice and business, and petty bureaucrats) have not taken kindly to the field of pure scientific endeavour.

The Turnbull government has continued what the previous government did: savage the fund lines, turning off the taps. Australia's core scientific institution risks becoming a rump, while other countries pour money into theirs with intoxicating enthusiasm.

The climate change modelling unit at the main scientific organisation, CSIRO, has been devastated, with the government feeling that sufficient work has been done in the area. Having tooted the Australian horn of achievement, Turnbull and scientific management feel that money might be better spent elsewhere.

The entire sense of Australian science as business can be gathered by a skirt through the website. The reader stumbles across the "Operating Model" which was obviously written by a technocrat versed in painful MBA jargon: "Our operating model underpins the successful execution of our strategy and delivery of our goals."[1]

The language is cold and uninspiring. There is a reminder where the body comes from, notably the provisions of the Science and Industry Research Act 1949. The message from the minister speaks about government "providing the catalyst for collaboration and transformation of our industries while capitalising on the depth of our innovative and highly skilled workforce."[2]

There is nothing in the minister's statement of 2015 (that of Ian Macfarlane of Industry and Finance) that reflects the deeper values of the scientific enterprise as science per se. Scientists are encouraged to foster business acumen, charging into brave futures with bright advertising credentials.

The idea is to reward Australian "industry" rather than add to the annals of discovery. What is sovereign is never in dispute. It is made clear that CSIRO "had a central role in the translation of science and technology into products and services that benefit our nation and enhance our productivity and our prosperity."

Policy documents that would have sat very comfortably in a Soviet government ministry have been produced, proclaiming strategic directions and aspirations. Strategy 2020: Australia's Innovation Catalyst, is one such ghastly product, glowingly administrative and heavily managerial.

CSIRO chief executive Larry Marshall's statement from 2015 uses all the language of spin in his vision. There are "inputs"; there are "crowd sourced ideas from more than 7000 of our creative people, customers, thought leaders and the public". There is that word that Australia's Prime Minister, Malcolm Turnbull, has made a Tibetan mantra: innovation.

For Marshall, the CSIRO is a business mechanism with a purpose. The body must "help reinvent existing industries and strive to create a new industry for a changing Australian economy." His message is delivered like a party official in full regalia. "Australia must be a high performing innovation economy."

This is emphasised in the CSIRO's overview of "global megatrends". Some mention is made about scarcity and resources, the issue of water, mineral and food resources. Climate change is briefly mentioned as part of the changes in earth systems "from global to microbial". (Such vagueness is typical in business speak.)

Economic worth makes a far more prominent appearance, to such an extent there is a mention of the "silk highway" (an insertion of Chinese influence?) seeing fast "growth of emerging economies, urbanisation, geopolitical change and the transition from industrialisation into technologically advanced service sectors."

Employees of CSIRO have also been caught off guard by the organisation's greater insistence that they strap on their entrepreneurial boots and seek out prospects to "partner" with business. "The CSIRO," as the organisation statement asserts, "invests in an evolving portfolio of businesses to deliver on our mission."

Australia's tertiary sector is also milking this tendency, creating a hybrid graduate interested in both scientific trends and business. The University of Technology Sydney, the University of New South Wales, and the Queensland University of Technology are among such institutions. The assumption here is that such hybrid degrees and combinations are automatic, and while it would be incorrect to ignore that science has economic and social applications, it is also a very narrow way of viewing the world.

Marshall's money-driven overview is a reminder about how subordinate science can become. It continues to prove central to the military industrial complex. It continues to fund projects of biosecurity that involve mass extermination of undesirable species (undesirable, in that sense, being determined as a matter of agrarian economy). University departments, strung along by industry grants, have also fallen victim to this cycle of production and discovery. Farewells have been made to genuine, speculative science. If an Einstein was to appear at the doorstep of CSIRO these days, he would be turned back with disdain. That is modern innovation for you.

Dr. Binoy Kampmark was a Commonwealth Scholar at Selwyn College, Cambridge.
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Notes
[1] http://www.csiro.au/en/About/Strategy-structure/Operating-model
[2] http://www.csiro.au/strategy/

The Journal of Orthomolecular Medicine Vol. 9, No.4 • 1994

The Adverse Effects of Food Additives on Health: A Review of the Literature with Special Emphasis on Childhood Hyperactivity

By Tuula E. Tuormaa

Introduction [excerpts]

A food additive is any substance not commonly regarded or used as food, which is added to, or used in or on, food at any stage to affect its keeping quality, texture, consistency, taste, colour, alkalinity or acidity, or to serve any other technological function in relation to food, and includes processing aids in so far as they are added to or used in or on food.1,2 Food additives in use today can be divided roughly into three main types: cosmetics, preservatives and processing aids, totalling presently about 3,794 different additives, of which over 3,640 are used purely as cosmetics, 63 as preservatives and 91 as processing aids.3 The growth in the use of food additives has increased enormously in the past 30 years, totalling now over 200,000 tonnes per year.45 Therefore it has been estimated that as today about 75% of the Western diet is made up of various processed foods, each person is now consuming an average 8-10 lbs of food additives per year, with some possibly eating considerably more.5"7 With the great increase in the use of food additives, there also has emerged considerable scientific data linking food additive intolerance with various physical and mental disorders, particularly with childhood hyperactivity.8"31

Childhood Hyperactivity

It is clear that the definition and the diagnosis of Childhood Hyperactivity, which have been varyingly also labelled as Attention Deficit Disorder, Minimal- or Cerebral Brain Dysfunction Disorder, Hyperkinesis etc., has been rather imprecisely defined in the medical literature.25,29,32,33 One explanation why this syndrome, which will be called here by its more popular name, hyperactivity, seems to be so poorly understood may stem from the fact that its diagnostic criteria differs considerably from one country to another.32-33 However, in general terms, the diagnosis of hyperactivity is usually applied to childhood behavioural disorders with quite a diverse symptomatology, which include; distractibility, poor tolerance to frustration, temper tantrums, excitability, aggression, difficulties with co-ordination, lability of mood, anxiety, impulsiveness, inattentive-ness, and disabilities with both cognitive and learning functions.32-33 In short, the diagnostic criteria of hyperactivity seem to cover a substantial proportion of children usually seen in child psychiatric practice.34

Hyperactivity from Infancy to Adulthood

Retrospective studies have shown that children diagnosed as hyperactive as an infant had suffered considerably more from varied health/behavioural problems than nonhyperactives.32,44 For example, a research database on 357 hyperactive children, based at Surrey University, showed that 82% of them were already extremely restless as an infant, 61 % suffered from poor and irregular sleep patterns, 75% displayed excessive crying or screaming, 52% rejected any contact or affection, 50% were poor feeders, 74% seemed to have an exaggerated thirst and 67% suffered from colic.45

Hyperactive toddlers, on the other hand, are described as children who never walk but run, are incapable of playing with any object for more than few seconds, and who combine unnaturally impulsive behaviour with a complete lack of any apprehension or fear.32 When at school, these children are usually extremely restless, inattentive, distractable and frequently display aggressive and anti-social tendencies.32-45 Primarily because of these behavioural problems, their academic school performance is generally poor and failed school grades are not uncommon. In fact follow-up studies of young adolescents diagnosed as hyperactives when children have shown, when compared to controls, a significantly higher drop-out and expulsion rate from schools,4649 a greater involvement in both drug and alcohol abuse,4851 a higher rate of motor vehicle accidents,48 a greater risk of developing criminal tendencies, as well as appearing before courts.48,49,52

For example one follow up study on 64 adolescents diagnosed hyperactive when children, showed that when they reached ages 17 to 25 years, 25% of them were still engaged in antisocial and delinquent behaviour.53,54 Similar findings have also been observed by other investigators.55-56 In short, the prognosis of hyperactive children, when they mature into adulthood, seems to be relatively poor. Despite an apparent decrease in the ratings of hyperactivity over the years, as adolescents and adults they still seem to continue to use impulsive rather than reflective approaches to cognitive tasks, are still distractable, generally emotionally immature, have a poor self-image and are frequently unable to maintain goals.52-57

Some Food Additives and Their Side-Effects
Cosmetics; Dyes/Colourants

Tartrazine (E102), which is primarily used by the soft drink industry, is one of the colours most frequently implicated in food intolerance studies.2,5,16,31,33,48,94-102 Adverse reactions to tartrazine seem to occur most commonly in subjects who are also sensitive to acetylsalicylic acid (ASA), a finding which was also observed by Feingold and his team. Depending on the test protocol followed, it has been found that between 10-40% of aspirin-sensitive patients are indeed usually also affected by tartrazine,101 the reactions including asthma,2,95,101-104 urticaria,2,99,101-105 rhinitis102-104 and, as previously mentioned, childhood hyperactivity.9-13

This may come about because the chemical structure of the tartrazine molecule has similar features to those of benzoates, other azo compounds, pyrazole compounds and the hydroxy-aromatic acids, which also include salicylates.2 Furthermore, it has been established that the azo compounds can be reduced in the intestine and in the liver,106,107 indicating that one of the several routes through which these molecules, too small to be antigenic in themselves, may act as a hapten, thus conjugating a larger molecule to form an antigenic compound.2,108,109

A major breakthrough in the understanding of the mechanisms involved in ASA intolerance came also with discovery that aspirin, including other non-steroidal antiinflammatory drugs, inhibit the synthesis of prostaglandins, by selectively blocking the cyclo-oxinase pathway, resulting in an enhanced production of leucotrienes.110-112 An excessive leucotriene production in turn leads to vascular permeability, causing oedema and inflammation, which is directly associated with various airway constriction disorders, including asthma.2,113,114

One study found that an oral administration of 50mg tartrazine to 122 patients suffering from allergy-related disorders, evoked the following reactions; feeling of suffocation, weakness, heat sensation, palpitations, blurred vision, rhinorrhoea, pruritus and urticaria. Even though 50mg could be considered as a substantial dose, such a quantity of tartrazine could easily be consumed by an individual drinking only a few bottles of soft drinks per day.96

Another carefully conducted double-blind placebo- controlled trial on 76 children diagnosed as hyperactive, showed that tartrazine and benzoates provoked abnormal behaviour patterns in 79% of them.29 In addition, a double-blind placebo-controlled trial on 10 hyperactive children when compared to controls, found that tartrazine increases urinary zinc secretion, and decreases serum and salivary zinc concentration in the hyperactives, with a corresponding deterioration in their behaviour. This phenomena was not found among the controls.

It was suggested therefore that tartrazine seems to act as a zinc chelating agent in susceptible individuals. Furthermore, that zinc depletion may also be one of the potential causes of childhood hyperactivity.100

Although tartrazine seems to be most frequently associated with adverse reactions,115 there are also other colouring agents which are known to cause mental and/or physical ill-effects.33,116

Curcumin (E100), used mainly in flour confectionery and margarine, has been found to cause mutations in bacteria and when fed to pigs, it increased the weight of their thyroid glands causing, in high doses, severe thyroid damage.533

Sunset Yellow (E110), used in biscuits, has been found to damage kidneys and adrenals when fed to laboratory rats.33 It has also been found to be carcinogenic when fed to animals.5

Carmoisine (El22), used mainly in jams and preserves, was found by the US Certified Color Manufacturers Association to be unavoidably contaminated with low levels of beta- napthylamine, which is a well known carcinogen;33 it has also been found to be mutagenic in animal studies.5

Amaranth (El23) has been found, when fed to laboratory rats, to cause cancer, birth defects, still births, sterility and early foetal deaths. Subsequent work has also found that amaranth can cause female rodents to reabsorb some of their own foetuses.5-33

Ponceau 4R (El24), used mainly in dessert mixes, has been found to exhibit a weak carcinogenic action.533

Erythrosine (E127), used in candied cherries and childrens' sweets, has been found to act as a potent neurocompetitive dopamine inhibitor of dopamine uptake by nerve endings when exposed in vitro on a rat brain.117 Other studies have shown that erythrosine can have an inhibitory action also on other neurotransmitters, resulting in an increased concentration of neurotransmitters near the receptors, thus functionally augmenting the synaptic neurotransmission.118120

There is now some evidence that a reduced dopamine turnover may lead to childhood hyperactivity.121 Similar findings have been linked with a reduction of noradrenaline.122 Erythrosine also has been found to have a possible carcinogenic action when tested on animals.5

Caramels (E150), of which over 100 different formulations are currently in use, are widely used by the cola drinks industry, as well as the beer and alcohol industry. It is also used as a colouring agent in crisps, bread, sauces, gravy browning etc.

The main recurring problem about the safety of caramels concerns the presence of an impurity called 4-Methylimidazole, produced by processes using ammonia, which leads to convulsions when fed to rats, mice and chicks. It has been also found that ammoniated caramels can affect adversely the levels of white blood cells and lymphocites in laboratory animals. Furthermore, a study on rabbits provided evidence that even small doses of ammoniated caramels seem to inhibit the absorption of vitamin B6.33

Brown FK is mainly used as a colouring agent in fish, such as kippers. Two of the primary metabolites of this colouring have been found to act as a cardiotoxin. It has been also observed, when fed in the long term to mice, to cause potentially hazardous nodules to form in the liver. Furthermore it has been found to cause mutations in some bacteria, implying that it may also act as a mutagenic and/or carcinogenic agent in humans.5,33

Preservatives/Antioxidants

Benzoates (E210-E219), used mainly in marinated fish, fruit- based fillings, jam, salad cream, soft drinks and beer, have been found to provoke urticaria, angioedema and asthma.2-33123 Furthermore, they have also been directly linked with childhood hyperactivity.29

Sulphites (E220-E227), used mainly in dried fruits, fruit juices and syrups, fruit-based dairy deserts, biscuit doughs, cider, beer and wine, have been linked with pruritus, urticaria, angioedema and asthma.2,31,33,124,125 When fed to animals, sulphites have also been found to have a mutagenic action.5

Nitrates and nitrites (E249-E252), used in bacon, ham, cured meats, corned beef and some cheeses, have been found to cause headaches in susceptible individuals.125 In addition, these chemicals have been linked with cancer both in animal533 and human studies.126 They have also been found to be mutagenic when fed to mammals.5

Butylated hydroxyanisole - BHA (E320), used in soup mixes and cheese spread, has been found to be tumour-producing when fed to rats.127 In human studies it has been linked with urticaria, angioedema and asthma.233-128-129

Monosodium glutamate (MSG), a flavour enhancer, used in savoury foods, snacks, soups, sauces and meat products, has been associated with a conjunction of symptoms in susceptible individuals, such as severe chest and/or facial pressure and overall burning sensations, not unlike a feeling that the victim is experiencing a heart attack.48 MSG has been also found to precipitate a severe headache and/or asthma in susceptible individuals.130,131 In susceptible children MSG has been linked with epilepsy-type "shudder" attacks.132 In animal studies it has been found to damage the brains of young rodents.48

Sweeteners

Saccharin, used as sweetening tablets and widely used by the soft drink and sweet food industry, has been shown to produce cancer when tested on animals.68,133-135 Saccharin has also been found to be mutagenic68,136,137 and growth inhibiting,'38 as well causing congenital malformations in animal studies.139

The fact that any substance which has been found to be carcinogenic also seems to have a mutagenic action, was established by testing 300 different carcinogenic chemicals for mutagenicity. The results showed that of the 300 carcinogenic chemicals tested, 90% were also found to have a mutagenic action.140

Aspartame, of which the key ingredient is the amino acid phenylalanine, is also widely used by the soft drink and sweet food industry. When fed to rats, aspartame was found to double the level of phenylalanine in their brains, which re-doubled when other carbohydrates were consumed at the same time. This combination was found to give a great rise in brain tyrosine, followed by a considerable reduction in brain tryptophan levels.141,142 Low tryptophan levels have been directly linked with both aggressive and violent behaviour.143-149

Furthermore, as dietary tryptophan acts as a precursor for serotonin (5-hydroxytrytamine, 5HT), reduced tryptophan levels will also result in a reduction of brain serotonin levels, which has been directly linked with both hyperactive and aggressive behaviour.150155

Sucrose/table sugar, which is a simple molecular substance artificially refined from complex carbohydrates, thus called a refined carbohydrate, can be found in most of our foods. An excessive refined carbohydrate consumption has been directly associated with a high incidence of both criminal and antisocial behaviour.28-47

Schoenthaler and his team conducted several double- blind, design-over studies among thousands of incarcerated juvenile offenders, finding a clear correlation between high sucrose/junk food intake and the incidence of antisocial behaviour. In all studies the primary dietary revision to reduce sugar consumption was organised by simply replacing sugary drinks and junk food snacks with fruit juices and nutritious snacks, such as nuts and fresh fruits.

After implementing this simple dietary policy with 276 incarcerated offenders, informal disciplinary actions were lowered 48%, when contrasting the twelve months before, and after nutritional revision. Assault and battery was lowered 82%, theft 77%, horseplay 65% and refusal-to-obey-an-order 55%.156,157

When similar diet policy was designed for 1382 offenders confined in three different juvenile institutions, there was a clear 25% reduction in rule violations. All 1382 juveniles served as their own controls and the length of the pre- and post-intervention period lasted for three months each.158

Similar findings were observed when the behaviour of 2005 incarcerated offenders was analyzed for 24 months. In the second half of the experiment i.e. after 12 months of the initial observation period, the offenders were no longer allowed foods/drinks containing sucrose or artificial additives; instead they were offered nuts, fruit, and fruit juices. After implementing the low-sugar diet policy the incidence of rule violations fell 21%, assaults and fights 25% and general disruptions 42%.159

The consumption of sucrose/additive-rich foods was not only seen to worsen the behaviour of young offenders, but when given to children diagnosed as hyperactive, these foods seemed greatly to increase their restless and destructive behaviour.160161

Similar results were established among a group of normal pre-school children, as sucrose was found significantly to correlate with their "inappropriate behaviour" pattern.162

An excessive refined carbohydrate consumption can also lead in susceptible individuals to a disordered carbohydrate metabolism, especially to reactive hypoglycaemia,163,164 which in turn has been found to be particularly prevalent among violent offenders.28,164-176 Reactive hypoglycemia has also been associated with diverse personality and psychiatric disorders, such as neuroses, panic attacks, agoraphobia and schizophrenic episodes.177

Full Text with 235 references

http://orthomolecular.org/library/jom/1994/articles/1994-v09n04-p225.shtml

The International Journal Of Hygiene And Environmental Health • January 2016

Non-phthalate plasticizers in German daycare centers and human biomonitoring of DINCH metabolites in children attending the centers (LUPE 3)

Author information

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Abstract

Plasticizers have been widely used for decades as additives in diverse applications, including consumer and building products, toys, cables, and floorings. Due to toxicological concerns and restrictions of different dialkyl ortho-phthalates, other plasticizers have been increasingly used in recent years. Therefore, di-isononyl cyclohexane-1,2-dicarboxylate (DINCH), di(2-ethylhexyl) terephthalate (DEHT), di(2-ethylhexyl) adipate (DEHA), acetyl tri-n-butyl citrate (ATBC), and trioctyl trimellitate (TOTM) plasticizer levels in indoor air and dust samples from 63 daycare centers in Germany were measured. Moreover, the urine samples of 208 children who attend 27 of these facilities were analyzed for the presence of four DINCH metabolites. DINCH, DEHT, and DEHA were present in indoor air with median values of 108 ng/m(3), 20 ng/m(3), and 34 ng/m(3), respectively. Median values of 302 mg/kg for DINCH, 49 mg/kg for DEHA, 40 mg/kg for DEHT, and 24 mg/kg ATBC were found in dust. In the urine samples, the three secondary metabolites of DINCH were observed with median values (95th percentiles) of 1.7 µg/l (10.0 µg/l) for OH-MINCH, 1.5 µg/l (8.0 µg/l) for oxo-MINCH, and 1.1 µg/l (6.1 µg/l) for cx-MINCH. Overall, these metabolite levels are orders of magnitude lower than the current HBM I values set by the German Human Biomonitoring Commission. Using general exposure assumptions, the intake resulting from dust ingestion and inhalation is low for children. The total daily DINCH intake calculated from biomonitoring data was 0.5 µg/kg b.w. using median values and 9.8 µg/kg b.w. as the maximum value. At present, non-phthalate plasticizers, especially DINCH, can be found in considerable amounts in dust samples from daycare centers and as DINCH metabolites in the urine of children. In relation to previous studies, the concentrations of DINCH in dust and urine have an increasing time trend. Compared with tolerable daily intake values, the total daily intake of DINCH reached only 1% of its maximum value to date; however, due to its increased use, higher exposure of DINCH is expected in the future.

http://www.ncbi.nlm.nih.gov/pubmed/26338253

“At present, non-phthalate plasticizers, especially DINCH, can be found in considerable amounts in dust samples from daycare centers and as DINCH metabolites in the urine of children. In relation to previous studies, the concentrations of DINCH in dust and urine have an increasing time trend.”

di-isononyl cyclohexane-1,2-dicarboxylate • DINCH • See Next Page

DINCH
1,2-Cyclohexane dicarboxylic acid diisononyl ester

1,2-Cyclohexane dicarboxylic acid diisononyl ester is a plasticizer for the manufacture of flexible plastic articles in sensitive application areas such as toys, medical devices and food packaging. From a chemical point of view it belongs to the group of aliphatic esters. In 2002 BASF started selling 1,2-cyclohexane dicarboxylic acid diisononyl ester under the tradename of Hexamoll DINCH as an alternative for phthalate plasticizers.

FOOD CONTACT

In the European Union the European Food Safety Authority has approved 1,2-cyclohexane dicarboxylic acid diisononyl ester for a wide variety of food contact applications in October 2006. In 2007 1,2-cyclohexane dicarboxylic acid diisononyl ester has been added to Annex III of the “Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with food”. The EU Directive 2002/72 has meanwhile been superseded by Regulation (EU) No. 10/2011. Hexamoll DINCH had been included by its chemical name in “Recommendations” I.

TOYS

A US federal law was passed in 2008 banning the use of some phthalates in children’s toys. When the law took effect in February 2009, Mattel and Learning Curve confirmed to NPR they were substituting phthalates with Hexamoll DINCH and citrate-based plasticizers. In the European Union 1,2-cyclohexane dicarboxylic acid diisononyl ester is not listed in directive 2005/84/EC which bans the use of certain phthalates in toys and childcare articles and thus can be used safely in toy and childcare articles there too.

“These results suggest that organ-specific responses to oxidative stress by these potential prooxidant compounds may implicate a mechanism of their toxicities.”

Toxicology Letters • January 2016

Oxidative stress response in canine in vitro liver, kidney and intestinal models with seven potential dietary ingredients

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Abstract

In vitro cell culture systems are a useful tool to rapidly assess the potential safety or toxicity of chemical constituents of food. Here, we investigated oxidative stress and organ-specific antioxidant responses by 7 potential dietary ingredients using canine in vitro culture of hepatocytes, proximal tubule cells (CPTC), bone marrow-derived mesenchymal stem cells (BMSC) and enterocyte-like cells (ELC). Cellular production of free radical species by denatonium benzoate (DB), epigallocatechin gallate (EPI), eucalyptol (EUC), green tea catechin extract (GTE) and sodium copper chlorophyllin (SCC), tetrahydroisohumulone (TRA) as well as xylitol (XYL) were continuously measured for reactive oxygen/nitrogen species (ROS/RNS) and superoxide (SO) for up to 24h. DB and TRA showed strong prooxidant activities in hepatocytes and to a lesser degree in ELC. DB was a weak prooxidant in BMSC. In contrast DB and TRA were antioxidants in CPTC. EPI was prooxidant in hepatocytes and BMSC but showed prooxidant and antioxidant activity in CPTC. SCC in hepatocytes (12.5mg/mL) and CPTC (0.78mg/mL) showed strong prooxidant and antioxidant activity in a concentration-dependent manner. GTE was effective antioxidant only in ELC. EUC and XYL did not induce ROS/RNS in all 4 cell types. SO production by EPI and TRA increased in hepatocytes but decreased by SCC in hepatocytes and ELC. These results suggest that organ-specific responses to oxidative stress by these potential prooxidant compounds may implicate a mechanism of their toxicities.

http://www.ncbi.nlm.nih.gov/pubmed/26602166

“These data suggest that the form of protein in infant formula may impact cognitive development and that the higher free amino acid content in breast milk may be a contributing factor to the differential cognitive development between breastfed and cow milk formula-fed infants.”

Amino Acids • March 2016

Effects of cow milk versus extensive protein hydrolysate formulas on infant cognitive development

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Abstract

Little research has focused on infant developmental effects, other than growth, of formulas that differ substantially in the form of protein. To examine development of infants fed formulas differing in free amino acid content, we randomized 0.5-month-old infants (n = 79) to either a control group who fed only cow milk formula (CMF) during the first 8 months (CMF8), or to one of two experimental groups: one experimental group fed extensively protein hydrolyzed formula (EHF) for 1-3 months during first 4.5 months (EHF1-3) of life, and the other fed EHF for 8 months (EHF8). The Mullen Scales of Early Learning were administered monthly from 1.5 to 8.5 months to assess fine (FM) and gross (GM) motor control, receptive (RL) and expressive (EL) language, visual reception (VR), and an early learning composite (ELC). Across the 5.5-8.5-month time period, when compared to CMF8 infants, GM scores in EHF1-3 infants averaged 1.5 points higher (95 % CI 0.1, 3.0) and in EHF8 infants 2.2 points higher (95 % CI 0.3, 4.0). Similarly, VR scores averaged 1.9 points higher (95 % CI 0.1, 3.8) in EHF1-3 infants and 2.2 points higher (95 % CI -0.2, 4.5) in EHF8 infants. EHF8 infants' RL scores averaged 1.8 points lower (95 % CI 0.1, 3.6) than CMF8 infants. These data suggest that the form of protein in infant formula may impact cognitive development and that the higher free amino acid content in breast milk may be a contributing factor to the differential cognitive development between breastfed and CMF-fed infants.

CLINICAL TRIAL REGISTRATION: clinicaltrials.gov NCT00994747

http://www.ncbi.nlm.nih.gov/pubmed/26497857

Clinical Pediatrics (Philadelphia, USA) • March 2016

A Critical Review of the Marketing Claims of Infant Formula Products in the United States

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Abstract

"A highly competitive infant formula market has resulted in direct-to-consumer marketing intended to promote the sale of modified formulas that claim to ameliorate common infant feeding problems. The claims associated with these marketing campaigns are not evaluated with reference to clinical evidence by the Food and Drug Administration. We aimed to describe the language of claims made on formula labels and compare it with the evidence in systematic reviews. Of the 22 product labels we identified, 13 product labels included claims about colic and gastrointestinal symptoms. There is insufficient evidence to support the claims that removing or reducing lactose, using hydrolyzed or soy protein or adding pre-/probiotics to formula benefits infants with fussiness, gas, or colic yet claims like "soy for fussiness and gas" encourage parents who perceive their infants to be fussy to purchase modified formula. Increased regulation of infant formula claims is warranted."

http://www.ncbi.nlm.nih.gov/pubmed/26054781

Environmental Geochemistry And Health • June 2016

The role of ions, heavy metals, fluoride, and agrochemicals: critical evaluation of potential aetiological factors of chronic kidney disease of multifactorial origin (CKDmfo/CKDu) and recommendations for its eradication

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Abstract

"The pollution of water and food through human waste and anthropogenic activities, including industrial waste and agricultural runoff, is a mounting problem worldwide. Water pollution from microbes causes identifiable diarrhoeal illnesses. The consumption of water contaminated with heavy metals, fluoride, and other toxins causes insidious illnesses that lead to protracted, non-communicable diseases and death. Chronic kidney disease of unusual/uncertain/unknown aetiology is one such example, began to manifest in the mid-1960s in several dry-zonal agricultural societies in developing economies that are located around the equator. In Sri Lanka, such a disease is affecting the North Central Province, the rice bowl of the country that first appeared in the mid-1990s. Several potential causes have been postulated, including heavy metals, fluoride, cyanobacterial and algae toxins, agrochemicals, and high salinity and ionicity in water, but no specific source or causative factor has been identified for CKD of multifactorial origin (CKDmfo). Three large studies conducted in the recent past failed to find any of the postulated components (heavy metals, cyanobacterial toxins, fluoride, salinity, or agrochemicals) at levels higher than those deemed safe by the World Health Organization and the US Environmental Protection Agency. At the reported low levels in water and with the heterogeneous geographical distribution, it is unrealistic to expect any of these components individually could cause this disease. However, the additive or synergistic effects of a combination of factors and components, even at lower exposure levels, together with malnutrition and harmful behaviours, and/or a yet-unidentified (or not investigated) toxin, can cause this epidemic. Because the cause is unknown, scientists need to work on broader hypotheses, so that key causative elements are not missed. Taken together the plausibility of multiple factors in the genesis of this disease, the appropriate terminology is CKDmfo, a name that also indicates the need for multidisciplinary research programs to facilitate identifying the cause(s) and the need for multiple approaches to eradicate it. While some potential causes remain to be investigated, existing data point to polluted water as the main source of this disease. This article evaluates pros and cons of each hypothesis and highlights the importance of among others, providing clean water to all affected and surrounding communities. Available data do not support any of the postulated agents, chemicals, heavy metals, fluoride, salinity/ionicity, or individual agrochemical components, such as phosphate or glyphosate, as causative factors for CKDmfo in Sri Lanka. However, as the CKDmfo name implies, a combination of these factors (or an unknown toxin) together with harmful behaviour and chronic dehydration may cause this disease. Irrespective of the cause, prevention is the only way forward for eradication."

http://www.ncbi.nlm.nih.gov/pubmed/26462963

“The FF [protein digestibility of a specific fermented nutritional food product] in piglets had a significantly higher apparent ileal crude protein digestibility than the SF [standard fermented] and HF [extensively hydrolyzed protein] and displayed lower ileal proteolytic activity than the SF [standard fermented]. Both effects may contribute to the alleviation of functional gastrointestinal symptoms reported in infants fed fermented infant milk formula.”

Journal Of Nutrition • July 2015

Fermented Infant Formula Increases Ileal Protein Digestibility and Reduces Ileal Proteolytic Activity Compared with Standard and Hydrolyzed Infant Formulas in Piglets

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Abstract

BACKGROUND

An infant formula that contained milk fermented by the bacteria Bifidobacterium breve and Streptococcus thermophilus (Lactofidus) was reported to alleviate functional digestive symptoms in infants. It was hypothesized that improved protein digestibility of the fermented infant formula could contribute to this effect.

OBJECTIVE

The aim of this study was to evaluate the protein digestibility of a specific fermented (FF), a standard (SF), and an extensively hydrolyzed protein (HF) formula.

METHODS

Four-week-old piglets (n = 7) were fitted with a T-cannula at the terminal ileum and received each formula in a Latin square design. FF, SF, and HF contained 11.7%, 9.3%, and 11.9% (w/w) crude protein; 1.5%, 5.4%, and 5.6% (w/w) fiber; and had a casein/whey ratio of 60:40, 50:50, and 0:100 per kilogram of powder, respectively. Ileal digesta were collected and analyzed for amino acids and proteolytic activity.

RESULTS

FF had a significantly higher apparent ileal crude protein digestibility (92.1% ± 1.0%) than SF and HF (84.4% ± 1.0% and 83.9% ± 0.9%, respectively). FF also had a significantly higher dry matter digestibility than SF and HF. The ileal crude protein flow of FF was significantly lower than that of SF and HF. The ileal flow of FF total proteolytic activity was significantly lower than that of SF but not significantly different from that of HF (412 ± 163 kU/8 h vs. 1530 ± 163 and 703 ± 156 kU/8 h, respectively).

CONCLUSIONS

The FF in piglets had a significantly higher apparent ileal crude protein digestibility than the SF and HF and displayed lower ileal proteolytic activity than the SF. Both effects may contribute to the alleviation of functional gastrointestinal symptoms reported in infants fed fermented infant milk formula.

http://www.ncbi.nlm.nih.gov/pubmed/26019249

(See: this chapter, report published in August of 2004, by H. Thibault)

“We showed that an high-fat, high-sucrose diet is able to promote Non-alcoholic fatty liver disease, and our results suggest that o-coumaric acid and berberine are promising complementary supplements that can ameliorate the metabolic disorders associated with an high-fat, high-sucrose diet; however, quercetin requires further investigation.”

Lipids In Health And Disease • July 2015

Effect of a high fat, high sucrose diet on the promotion of non-alcoholic fatty liver disease in male rats: the ameliorative role of three natural compounds

Ragab SM1, Abd Elghaffar SKh2, El-Metwally TH3, Badr G4, Mahmoud MH5,6, Omar HM7.

Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a multifactorial disease with a complex pathophysiology. The clinical features of NAFLD include obesity, insulin resistance (IR) and dyslipidemia. Consumption of a diet high in saturated fats and sucrose is an important factor in the increasing occurrence of these metabolic disorders, primarily NAFLD and IR. We sought to assess the role of a high-fat, high-sucrose (HFS) diet in the promotion of NAFLD and to evaluate the effects of quercetin (Q), berberine (BB) and o-coumaric acid (CA) on modulation of these disorders.

METHODS

Fifty male rats were divided into 2 main groups as follows: group 1 comprised 10 rats fed a standard diet (SD), and group 2 comprised 40 rats fed an HFS diet for 6 weeks and then subdivided equally into 4 groups; one of these groups served as the HFS diet and each of the other three groups received daily supplementation with either Q, CA or BB for 6 weeks.

RESULTS

In the present study, several metabolic disorders were induced in our laboratory animal model, as evidenced by histological and biochemical changes. These alterations included serum and hepatic dyslipidemia (i.e., increased triglyceride, total cholesterol and low-density lipoprotein levels and decreased high-density lipoprotein levels), alterations in metabolic enzyme activities (lipase, glycerol-3-phosphate dehydrogenase, and glucose-6-phosphate dehydrogenase), histological changes in the liver (micro- and macrovesicular steatosis) and the downregulation of peroxisome proliferator-activated receptor y (PPARy) in adipose tissue and the liver. Daily oral supplementation with Q, CA or BB for 6 weeks after NAFLD induction had a hypolipidemic action and modulated metabolic markers.

CONCLUSION

We showed that an HFS diet is able to promote NAFLD, and our results suggest that CA and BB are promising complementary supplements that can ameliorate the metabolic disorders associated with an HFS diet; however, Q requires further investigation.

Full text, graphs, charts and 70 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4520282/

“Results suggest that the promotion of unhealthy commodity products during sporting matches is contributing to increased awareness amongst children of unhealthy commodity brands.”

BMC Public Health • October 2015

Children’s implicit recall of junk food, alcohol and gambling sponsorship in Australian sport

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Abstract

BACKGROUND

In Australia, sport is saturated by the promotion of junk food, alcohol and gambling products. This is particularly evident on player jerseys. The effect of this advertising on children, who are exposed to these messages while watching sport, has not been thoroughly investigated. The aim of this research study was to investigate: (1) the extent to which children implicitly recalled shirt sponsors with the correct sporting team; (2) whether children associated some types of sponsors with certain sporting codes more than others; and (3) whether age of the children influenced the correct recall of sponsoring brands and teams.

METHOD

This experimental study conducted in New South Wales, Australia used projective techniques to measure the implicit recall of team sponsorship relationships of 85 children aged 5-12 years. Participants were asked to arrange two sets of magnets - one which contained sporting teams and one which contained brand logos - in the manner deemed most appropriate by them. Children were not given any prompts relating to sporting sponsorship relationships.

RESULTS

Three quarters (77 %) of the children were able to identify at least one correct shirt sponsor. Children associated alcohol and gambling brands more highly with the more popular sporting code, the National Rugby League compared to the Australian Football League sporting code. Results showed that age had an effect on number of shirt sponsors correctly recalled with 9-12 year olds being significantly more likely than 5-8 year olds to correctly identify team sponsors.

CONCLUSIONS

Given children’s ability to implicitly recall shirt sponsors in a sporting context, Australian sporting codes should examine their current sponsorship relationships to reduce the number of unhealthy commodity shirt sponsors. While there is some regulation that protects children from the marketing of unhealthy commodity products, these findings suggest that children are still exposed to and recall these sponsorship relationships. Results suggest that the promotion of unhealthy commodity products during sporting matches is contributing to increased awareness amongst children of unhealthy commodity brands. Further investigation is required to examine the extent and impact of marketing initiatives during televised sporting matches on children.

Full text with 66 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4595000/

Trials • November 2015

Application effect of extensively hydrolyzed milk protein formula and follow-up in preterm children with a gestational age of less than 34 weeks: study protocol for a randomized controlled trial

Author information

Yin LP1, Qian LJ2, Zhu H3, Chen Y4, Li H5, Han JN6, Qiao LX7.

Abstract

BACKGROUND

The average incidence of preterm birth in the world is up to 11.1 %, and deaths of preterm children account for more than 50 % of neonatal deaths. Gastrointestinal function of preterm children with a gestational age less than 34 weeks is immaturely developed. For preterm children who can only be fed with formula due to their mothers' sickness, choosing a suitable formula can not only meet the high nutritional needs of preterm children, but also solve their low gastrointestinal tolerability, and is thus very important.

METHODS/DESIGN

The study is a prospective, randomized, single-blind and controlled clinical trial. Preterm children with a gestational age less than 34 weeks meeting the inclusion criteria who cannot be breastfed will be included. To demonstrate the application effect of extensively hydrolyzed milk protein formula on the target population, preterm children will be randomized into two groups, 185 subjects in each group. The observation group will be fed with extensively hydrolyzed milk protein (100 % whey protein) formula, while the control group will be fed with preterm children's formula until the children are discharged from the neonatal intensive care unit (NICU). All the formula involved in this study will be from Dumex. After discharge, both groups will be uniformly fed with formula for 0 to 6-month-old infants. For statistical analysis, a chi-square test and Student's t test will be applied using SAS 9.4.

DISCUSSION

This will be the first randomized controlled clinical study with long-term observation of the growth and development of preterm children during the NICU stay and at 3-month follow-up after discharge from the NICU. Results from this study will be used to determine whether the extensively hydrolyzed formula is more suitable for the low gastrointestinal tolerability of preterm children, and also whether feeding preterm children who are fed with such formula during the NICU stay with ordinary infant formula after discharge from the NICU would affect the normal growth and development of preterm children in the early stage of their lives.

TRIAL REGISTRATION

This study was registered with the Chinese Clinical Trial Registry
(http://www.chictr.org.cn/)
with number ChiCTR-IOR-14005696 ,
on December 22, 2014.

Full text, graphs, charts and 54 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632355/

THIS IS AN ONGOING REGISTERED TRIAL
No. ChiCTR-IOR-14005696

DISCUSSION

This will be the first randomized controlled clinical study with long-term observation of the growth and development of preterm children during the NICU stay and at 3-month follow-up after discharge from the NICU. Results from this study will be used to determine whether the extensively hydrolyzed formula is more suitable for the low gastrointestinal tolerability of preterm children, and also whether feeding preterm children who are fed with such formula during the NICU stay with ordinary infant formula after discharge from the NICU would affect the normal growth and development of preterm children in the early stage of their lives.

Food Nutrition Research • December 2015

The anti-obesity effects of Lactobacillus casei strain Shirota versus Orlistat on high fat diet-induced obese rats

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Abstract

BACKGROUND

Obesity and overweight are major public health problems. Various factors, such as daily nutritional habits, physical inactivity, and genetic, are related to the prevalence of obesity. Recently, it was revealed that the gut microflora may also play an important role in weight management. Thus, this study aimed to determine the anti-obesity effects of Lactobacillus casei strain Shirota (LcS) compared with those of orlistat in an animal model fed a high-fat diet (HFD).

DESIGN

Thirty-two male Sprague-Dawley rats were assigned to four groups fed various diets as follows: a standard diet group, HFD group, HFD supplemented with LcS (108109 colony-forming units (HFD-LcS) group, and HFD group treated with Orlistat (10 mg/kg body weight)). After 15 weeks, the weights of organs, body weight, body fat mass and serological biomarkers were measured. In addition, histological analysis of the liver and adipose tissue was performed.

RESULTS

Body weight, body mass index, fat mass, leptin and glucose levels were lower, and high-density lipoprotein and adiponectin levels were higher in the HFD-LcS and HFD-orlistat groups than in the HFD group. In addition a significant difference in body fat mass was observed between HFD-LcS group with HFD-orlistat group (19.19±5.76 g vs. 30.19±7.98 g). Although the interleukin-6 level was significantly decreased in the HFD-LcS and HFD-orlistat groups compared with the HFD group, no significant change was observed in other inflammatory biomarkers.

CONCLUSION

The results of the present study show that LcS supplementation improves body weight management and the levels of some related biomarkers. In addition, LcS supplementation showed a better result in fat mass and alanine aminotransferase reduction than Orlistat. Further studies are needed to elucidate the anti-obesity effects of LcS, with a longer period of supplementation.

Full text, graphs, charts and 51 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856475/

Environment International • October 2014

Organophosphate flame retardants and plasticizers in the air and dust in German daycare centers and human biomonitoring in visiting children (LUPE 3)

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“Based on the 95th percentile in dust and air in our study and data from residences in a previously published study, the daily intake of the most abundant Organophosphate, Tri-(2-butoxyethyl)-phosphate (TBEP), is high. This level is approximately 6.4% of the reference dose established by the National Science Foundation, USA. Overall, our study shows that daycare centers are indoor environments that contribute to Organophosphate exposure.”

Abstract

Organophosphate (OP) flame retardants and plasticizers are chemicals that have been used in large quantities in diverse consumer and building-related products for decades. In the present study, OPs were measured in paired indoor air and dust samples from 63 daycare centers in Germany. Moreover, the urine of 312 children between 22 and 80 months old who attend these facilities was analyzed for the presence of eight OP metabolites. Tri-(2-butoxyethyl)-phosphate (TBEP), tris-(2-chloroisopropyl) phosphate (TCPP), and tri-n-butyl-phosphate (TnBP) were present in low concentrations in indoor air, with median values of 49 ng/m(3), 2.7 ng/m(3), and 2.2 ng/m(3), respectively. In dust, median values of 225 mg/kg for TBEP, 2.7 mg/kg for TCPP, 1.1mg/kg for diphenyl(2-ethylhexyl) phosphate, and 0.5mg/kg for triphenyl-phosphate (TPhP) were found. In the urine samples, the metabolites di-phenyl-phosphate, di-n-butyl-phosphate, and di-(2-butoxyethyl)-phosphate had median values (95th percentiles) of 0.8 µg/l (4.0 µg/l), 0.2 µg/l (0.9 µg/l), and 2.0 µg/l (10.7 µg/l), respectively. A significant correlation was found between the dust and air samples in the levels of TnBP, tris(2-chloroethyl) phosphate (TCEP), and TBEP. For TCEP and TBEP, significant correlations were also observed between the levels in dust and the respective metabolite levels in urine. For TCEP, there was also a significant correlation between the concentration in indoor air and metabolite levels in urine. Based on the 95th percentile in dust and air in our study and data from residences in a previously published study, the daily intake of the most abundant OP (TBEP) is high (i.e., 3.2 µg/kg b.w.). This level is approximately 6.4% of the reference dose (RfD) established by the NSF, U.S.A. Overall, our study shows that daycare centers are indoor environments that contribute to OP exposure.

http://www.ncbi.nlm.nih.gov/pubmed/25033099

BMC Public Health • February 2013

Food, fizzy, and football: promoting unhealthy food and beverages through sport— a New Zealand case study

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Abstract

BACKGROUND

High participation rates in sport and increasing recognition of how diet benefits athletic performance suggest sports settings may be ideal locations for promoting healthy eating. While research has demonstrated the effect of tobacco and alcohol sponsorship on consumption, particularly among youth, few studies have examined the extent or impact of food and beverage company sponsorship in sport. Studies using brand logos as a measure suggest unhealthy foods and beverages dominate sports sponsorship. However, as marketing goes beyond the use of brand livery, research examining how marketers support sponsorships that create brand associations encouraging consumer purchase is also required. This study aimed to identify the characteristics and extent of sponsorships and associated marketing by food and non-alcoholic beverage brands and companies through a case study of New Zealand sport.

METHODS

We conducted a systematic review of 308 websites of national and regional New Zealand sporting organisations to identify food and beverage sponsors, which were then classified as healthy or unhealthy using nutrient criteria for energy, fat, sodium and fibre levels. We interviewed 18 key informants from national and regional sporting organisations about sponsorships.

RESULTS

Food and beverage sponsorship of sport is not extensive in New Zealand. However, both healthy and unhealthy brands and companies do sponsor sport. Relatively few support their sponsorships with additional marketing. Interviews revealed that although many sports organisations felt concerned about associating themselves with unhealthy foods or beverages, others considered sponsorship income more important.

CONCLUSIONS

While there is limited food and beverage sponsorship of New Zealand sport, unhealthy food and beverage brands and companies do sponsor sport. The few that use additional marketing activities create repeat exposure for their brands, many of which target children. The findings suggest policies that restrict sponsorship of sports by unhealthy food and beverage manufacturers may help limit children's exposure to unhealthy food marketing within New Zealand sports settings. Given the global nature of the food industry, the findings of this New Zealand case study may be relevant elsewhere.

Full text, graphs, charts and 31 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3574844/

“While there is limited food and beverage sponsorship of New Zealand sport, unhealthy food and beverage brands and companies do sponsor sport.

The few that use additional marketing activities create repeat exposure for their brands, many of which target children.”

Danish Medical Journal • February 2013

Nutrition, growth, and allergic diseases among very preterm infants after hospital discharge

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Abstract

The aims of this PhD thesis were: 1. Primarily to investigate the effect, of adding human milk fortifier to mother's milk while breastfeeding very preterm infants after hospital discharge, on growth until 1 year corrected age (CA) 2. Secondarily to describe breastfeeding rate and factors associated with breastfeeding among very preterm infants at hospital discharge. 3. To describe possible feeding-problems during the intervention-period, and allergic diseases during the first year of life, among very preterm infants related to their nutrition after hospital discharge. 4. To describe the content of macronutrients in human milk from mothers delivering very preterm. This PhD thesis is based on a prospective, randomized, and controlled interventional birth cohort study. A total of 633 very preterm infants with a gestational age (GA) ≤ 32 + 0 weeks were recruited consecutively from July 2004 until August 2008 of whom 157 were excluded due to diseases or circumstances influencing nutrition. Further 156 refused participation in the interventional part of the study, but data on breastfeeding, weight, and some epidemiological data until discharge were available. Results on breastfeeding rate at discharge were therefore based on data from 478 infants, and parents of 320 infants accepted participation in the intervention study. Of these 320 infants, 207 were exclusively breastfed and they were shortly before hospital discharge randomized to either breastfeeding without (group A) or with fortification (group B) until 4 months CA. Infants (n = 113) who were bottle-fed at discharge (group C) were given a preterm formula (PF) until 4 months CA. Infants were examined at the outpatient clinics at term, and at 2, 4, 6, and 12 months CA, where parameters on growth, allergic diseases, possible feeding problems, blood-samples, and milk samples were obtained. Data on duration of exclusively breastfeeding and time of introduction to formula and/or complementary food were also recorded. Among the 478 infants 60% (n = 285) were exclusively breastfed, 35% (n = 167) were exclusively bottle-fed, and 5% (n=26) were both breast- and bottle-fed at discharge. Compared to mothers in lower social groups and mothers who smoked, mothers in higher social groups and "non-smokers" were significantly (p = 0.000 and p = 0.003 respectively) more often breastfeeding their very preterm infants at discharge. Single birth infants tended more often to be breastfed (p = 0.09). Infant age at discharge and duration of hospitalization did not influence breastfeeding at discharge. Increase in weight Z-score from birth to discharge was largest in the bottle-fed group compared to the breastfed group (p = 0.000), probably due to feeding practice the last week(s) of hospitalization. In the intervention study, 207 exclusively breastfed very preterm infants were randomized to group A (n = 102) and B (n = 105) respectively. The duration of breastfeeding was not influenced by fortification of mother's milk after hospital discharge. There was no significant difference on growth comparing group A and B at 12 months CA. Both boys and girls in group C achieved catch-up in weight and length earlier as compared to group A and B. Per protocol (PP) analysis showed that girls, but not boys, were longer and had a larger head circumference but were not heavier in group B (n = 51) compared to group A (n = 73) at 2 and 4 months CA (p<0.05). Protein-concentration in mothers' milk declined significantly from 2 weeks (1.8 g/100 ml) to 6 weeks after birth (1.4 g/100 ml) and declined further to 1.2 g/100 ml 12 weeks after birth. The incidence and the prevalence at 12 months CA of recurrent wheezing was 39.2% and 32.7% respectively, while atopic dermatitis was 18.0% and 12.1% respectively. Predisposition to allergic disease increased the risk of developing atopic dermatitis (p = 0.04) (OR 2.6 (95% CI 1.0-6.4)), and the risk of developing recurrent wheezing (p = 0.02) (OR 2.7 (95% CI 1.2-6.3)). Boys had an increased risk of developing recurrent wheezing (p = 0.003) (OR 3.1 (95% CI 1.5-6.5)). In conclusion breastfeeding can successfully be established in very preterm infants. Fortification of human milk after hospital discharge while breastfeeding was possible without influencing the duration of breastfeeding. Fortification in the amount given in this study did, however, not affect growth significantly at 1 year of age. An increased amount of protein was correlated with increased BUN-values indicating a better growth potential. Fortification of mother's milk or preterm formula was not associated with an increased risk of developing allergic diseases. Future follow-up of this cohort investigating e.g. growth, allergic diseases, and neuropsychological development is planned at 6 years of age. The definition of optimal growth and nutrition of preterm infants is though still a question for debate and further investigations are needed.

http://www.ncbi.nlm.nih.gov/pubmed/23461996

Volume 5 • 2012

Stanford Journal Of Animal Law And Policy

May Contain Hooves: Why and How the Government Should Implement Plain-Language Disclosure of Animal Products in Food Labels

Author Information

By Robert Glenn Ayres

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A large number of Americans are vegetarians or vegans due to ethical rather than dietary concerns. Current food labeling laws require affirmative disclosure of ingredients, but for a number of reasons often allow the use of ingredients which are or may be derived from animal or "slaughter" products, or the inclusion of minute amounts of such products as flavoring, without disclosure to the consumer, or even a reasonable means of discovery. Recent regulations, for instance the disclosure of potential allergens, show that there is a relatively simple means to correct this problem and do so with minimal disruption and cost to manufacturers.

Introduction

It is hardly a shocking revelation that Americans remain largely unaware of what goes into the food they eat. Processed foods make up a majority of the American diet,1 and a complex and interrelated series of government labeling laws and regulations require disclosure of most ingredients and the nutritional values of such products. However, such ingredients are often disclosed in highly technical language without notice of source, and requirements focused on nutrition often allow the undisclosed presence of minor flavoring ingredients.2 As a result, there is no federal guidance specifically addressing the issue of the undisclosed presence of food ingredients that may violate some consumers' ethical or religious dietary concerns. While certain specific religious food restrictions have led to much scholarly debate and, several state laws3, the idea of a more general system at the federal level to assist in ethical eating decisions has received comparatively little public consideration.

This absence is especially glaring in the case of vegetarians and vegans, who are regularly and almost certainly unknowingly exposed to foods containing non-vegetarian products such as gelatins processed from fish or the cartilage or hooves of slaughtered animals, shortenings, oleic compounds, and stearates derived from animals.

REFERENCES

1. This has been true since at least the early 1970s, and perhaps much longer. See generally Arthur Koch, The F.D.A. Knows-But Won't Tell: An Argument for Ingredient Labeling of Food Products, 21 J. PUB. L.281, 293 (1972).

2. To take a random, well-known example, the label on a bag of Cheetos lists about thirty ingredients as ferrous sulfate, autolyzed yeast extract, and disodium guanylate, in addition to inherently ambiguous ingredients such as enzymes and natural flavor. The author of this Article, despite being a former organic chemist, is by no means familiar with all the ingredients disclosed on a bag of cheese puffs.

3. See, e.g., Gerald F. Masoudi, Kosher Food Regulation and the Religion Clauses of the First Amendment, 60 U. CHI. L. REV. 667, 670 (1993).

4. See IAN LENDLER, ALCOHOLICA ESOTERICA 28 (Penguin Books, 2005) (noting how many modern brewers clarify beer using isinglass, a gelatin made from a sturgeon's bladder).

5. S. SUZANNE NIELSEN, ED., FOOD ANALYSIS 158 (Birkhäuser, 3d ed. 2003).

6 RUTH WINTER, A CONSUMER'S DICTIONARY OF FOOD ADDITIVES: DESCRIPTIONS IN PLAIN ENGLISH OF MORE THAN 12,000 INGREDIENTS BOTH HARMFUL AND DESIRABLE FOUND IN FOODS 514 (Random House, 7th ed. 2009).

7. Id. at 396.

“Ethanol accumulation in fresh cut apple slices increased significantly throughout the experimental period. Over all Rosmarinic Acid exhibited maximum effect in all the food preservation parameters studied suggesting that it has synchronized food protection effect and can be recommended as food additive.”

Pakistan Journal Of Biological Science • January 2012

Evaluation of food protective property of five natural products using fresh-cut apple slice model

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Abstract

The present study evaluated the antioxidant (AA), antimicrobial and preservation effects of five plant derived natural products viz., Rosmarinic Acid (RA), p-Coumaric Acid (pCA), Trans-Cinnamic Acid (TCA), Hydroxyphenyllactic Acid (HPA) and Caffeic acid (CA) along with synthetic compounds (Ascorbic acid, gallic acid, citric acid and BHA) on fresh cut apple slices. Antimicrobial efficacy of these compounds against Bacillus licheniformis, Pseudomonas vulgaris, Shigella boydii, Salmonella typhi, Staphylococcus aureus, Listeria monocytogenes and Escherichia coli was found to be concentration dependent with the maximum inhibition observed at 500 microg mL(-1). A considerable AA potential of these compounds was observed in in vitro based assay system, with RA exhibiting significantly higher effect than the other compounds at 500 microg mL(-1). Furthermore the compounds at 500 microg mL(-1) significantly reduced the browning, maintained the acidic pH and restricted growth of L. monocytogenes even after 10 days of treatment. Ethanol accumulation in fresh cut apple slices increased significantly throughout the experimental period. Over all RA exhibited maximum effect in all the food preservation parameters studied suggesting that it has synchronized food protection effect and can be recommended as food additive.

http://www.ncbi.nlm.nih.gov/pubmed/22530437

“Skin care products had the highest quantities of Chemicals of Emerging Concern, with titanium dioxide and zinc oxide nanomaterials being dominant potential contaminants.”

Environmental Technology • July 2012

Cosmetics as a potential source of environmental contamination in the UK

Author information

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Abstract

Chemicals of emerging concern (CECs) are frequently used in cosmetic formulations and can potentially reach the environment at concentrations that may cause harm. A methodology was developed to assess over 120 chemicals assembled from product ingredient listings to identify and validate potential CECs in cosmetics, based on Annex XIII of REACH legislation. Ten potential CECs were identified: polydimethylsiloxane, butylated hydroxylanisole (BHA), butylated hydroxytoluene, triclosan, nano titanium dioxide, nano zinc oxide, butylparaben, diethyl phthalate, octinoxate methoxycinnamate and benzophenone. These chemicals were quantified based on their consumption and concentrations in cosmetics and percentage market penetration. The initial predicted environmental concentrations (PEC initial) were estimated to determine their exposure to the environment. With the exception of BHA, the PEC initial highlighted levels of exposure to the environment that triggered the need for further investigation of the chemicals. These chemicals were linked to cosmetics to highlight products with the potential to cause environmental harm. Skin care products had the highest quantities of CECs, with titanium dioxide and zinc oxide nanomaterials being dominant potential contaminants. Further research is required to assess the exposure pathways and fate of these chemicals to determine environmental risks associated with their use and disposal.

http://www.ncbi.nlm.nih.gov/pubmed/22988620

Lipids In Health And Disease • January 2011

Animal products, diseases and drugs: a plea for better integration between agricultural sciences, human nutrition and human pharmacology

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Abstract

“Eicosanoids are major players in the pathogenesis of several common diseases, with either overproduction or imbalance (e.g. between thromboxanes and prostacyclins) often leading to worsening of disease symptoms. Both the total rate of eicosanoid production and the balance between eicosanoids with opposite effects are strongly dependent on dietary factors, such as the daily intakes of various eicosanoid precursor fatty acids, and also on the intakes of several antioxidant nutrients including selenium and sulphur amino acids. Even though the underlying biochemical mechanisms have been thoroughly studied for more than 30 years, neither the agricultural sector nor medical practitioners have shown much interest in making practical use of the abundant high-quality research data now available. In this article, we discuss some specific examples of the interactions between diet and drugs in the pathogenesis and therapy of various common diseases. We also discuss, using common pain conditions and cancer as specific examples, how a better integration between agricultural science, nutrition and pharmacology could lead to improved treatment for important diseases (with improved overall therapeutic effect at the same time as negative side effects and therapy costs can be strongly reduced). It is shown how an unnaturally high omega-6/omega-3 fatty acid concentration ratio in meat, offal and eggs (because the omega-6/omega-3 ratio of the animal diet is unnaturally high) directly leads to exacerbation of pain conditions, cardiovascular disease and probably most cancers. It should be technologically easy and fairly inexpensive to produce poultry and pork meat with much more long-chain omega-3 fatty acids and less arachidonic acid than now, at the same time as they could also have a similar selenium concentration as is common in marine fish. The health economic benefits of such products for society as a whole must be expected vastly to outweigh the direct costs for the farming sector.”

http://www.ncbi.nlm.nih.gov/pubmed/21247506

Environment International • February 2011

Analytical developments and preliminary assessment of human exposure to organophosphate flame retardants from indoor dust

Author information

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Abstract

“A new and efficient analytical method was developed and validated for the analysis of organophosphorus flame retardants (OPFRs) in indoor dust samples. This method involves an extraction step by ultrasonication and vortex, followed by extract clean-up with Florisil solid-phase extraction cartridges and analysis of the purified extracts by gas chromatography-mass spectrometry (GC-MS). Method recoveries ranged between 76 and 127%, except for volatile OPFRs, such as triethyl phosphate (TEP) and tri-(n-propyl) phosphate (TnPP), which were partially lost during evaporation steps. The between day precision on spiked dust samples was <14% for individual OPFRs, except for TEP, tri-iso-butyl phosphate (TiBP) and tri (2-butoxyethyl) phosphate (TBEP). Method limit of quantifications (LOQ) ranged between 0.02 μg/g (TnPP and tris(1-chloro-2-propyl phosphate (TCPP)) and 0.50 μg/g (TiBP). The method was further applied for the analysis of indoor dust samples taken from Flemish homes and stores. TiBP, TBEP and TCPP were most abundant OPFR with median concentrations of 2.99, 2.03 and 1.38 μg/g in house dust and of 1.04, 3.61, and 2.94 μg/g in store dust, respectively. The concentration of all OPFRs was at least 20 to 30 times higher compared to polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDs). Estimated exposure to OPFRs from dust ingestion ranged for individual OPFRs between <1 and 50 ng/kg body weight for adults and toddlers, respectively. The estimated body burdens were 1000 to 100 times below reference dose (RfD) values, except for the scenario with high dust ingestion and high concentrations of TBEP in toddlers, where intake was only 5 times below RfD. Exposure of non-working and working adults to OPFRs appeared to be similar, but in specific work environments, exposure to some OPFRs (e.g. TDCPP) was increased by a factor >5.”

http://www.ncbi.nlm.nih.gov/pubmed/21176966

Journal Of The Science Of Food And Agriculture • March 2011

Oxidative stability of cooked, frozen, reheated beef patties: effect of antioxidants

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Abstract

BACKGROUND

The effect of selected antioxidants (grape seed extract (GS), oleoresin rosemary (OR), water-soluble oregano extract (WO), propyl gallate (PG), butylated hydroxyanisole (BHA)), butylated hydroxytoluene (BHT)) on sensory, color and oxidative stability of cooked, frozen, reheated ground beef patties was evaluated. Beef lean and trim were ground; antioxidants and salt were added. Patties were cooked (71 °C), overwrapped in commercial polyvinyl chloride film, and stored frozen (-18 °C), then evaluated monthly for 6 months. Flavor, odor and color were determined using a descriptive panel. Instrumental color was determined by a spectrocolorimeter. Lipid oxidation was determined using thiobarbituric acid reactive substances (TBARS).

RESULTS

After 6 months of storage, PG and GS samples had lower rancid odor scores and TBARS than controls. Control samples and those containing BHT did not differ statistically in sensory grassy or rancid odor, indicating that they were the most oxidized. TBARS correlated with grassy, rancid, cardboard and beef odors during the 6-month storage period.

CONCLUSIONS

Based on TBARS, the order of effectiveness of the antioxidants was PG and GS > OR > BHA > WO and BHT > control. TBARS were well correlated with sensory evaluations of odor and flavor. Antioxidants also protected a* values during storage.

http://www.ncbi.nlm.nih.gov/pubmed/21254072

Gastroenterology And Hepatology Bed To Bench • Spring 2011

The impact of breakfast in metabolic and digestive health

Author information

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Abstract

AIM

The purpose of this study is to explore whether the types and quality of breakfast could influence energy levels (blood glucose levels) and propose ideal breakfast models.

BACKGROUND

It is widely considered that a regular breakfast provides a number of health benefits; however, there is no general scientific agreement regarding what kind of food should be consumed. Evidence supports the importance of balancing blood glucose levels by low glycaemic index/load (L-GI/L) and increased protein diets, in particular in metabolic disorders, which non-alcoholic fatty liver disease (NAFLD) has a close relation to.

PATIENTS AND METHODS

This study was conducted by using a valid and standard questionnaire at the University of Worcester to evaluate the breakfast and dietary habits and energy levels. The Kruskal-Wallis test was used for statistical analysis.

RESULTS

No significant differences were found either between breakfast consumption, energy levels, types of snack and amount of caffeine intake in the morning or between types of breakfast, energy levels, types of snack, and amount of caffeine intake in the morning. However, potential differences in energy levels were found across the groups of breakfast types: glycaemia (GL) ($p=.057$) and protein intake ($p=.056$).

CONCLUSION

The types and quality of breakfast would be key as regular breakfast consumption alone did not show adequate health benefits. Lower GL foods and higher protein intake at breakfast were found to be associated with higher energy levels. It is therefore recommended that breakfast foods should be low in GL and high in protein. These changes may lead to better health status and prevention of disease, especially metabolic and liver disorders, in the long term.

Full text, graphs, charts and 75 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017414/

“Establishing novel therapeutic interventions aimed at preventing and/or reducing in utero-induced insulin resistance and vascular dysfunction warrants investigation because the numbers of low birthweight babies continue to increase.”

Seminal Reproductive Medicine • May 2011

In utero origins of adult insulin resistance and vascular dysfunction

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Abstract

The metabolic syndrome (or syndrome X) is a constellation of risk factors including insulin resistance, hypertension, dyslipidemia, and central obesity that predispose to the development of cardiovascular disease and type 2 diabetes in adult life. Insulin resistance is believed to be a critical pathophysiological event early in the disease process, impacting both skeletal muscle metabolic function and vascular responses. Adverse changes in insulin sensitivity have been found to originate in utero; for instance, prenatal events such as placental insufficiency/oxidative stress leading to altered fetal growth trajectories are associated with increased rates of metabolic syndrome in adult life. Such intrauterine insults result in reduced skeletal muscle mass in conjunction with altered insulin signaling, decreased oxidative fibers, and impaired mitochondrial function. These developmental disturbances set the stage for development of muscle triglyceride accumulation and depressed insulin sensitivity in childhood. Abnormalities of vascular structure and function arising from deprived intrauterine conditions that are exacerbated by insulin resistance account for the progression of hypertension from childhood to adulthood. Arterial changes initiated in utero include reduced endothelial nitric oxide (NO) bioavailability, vascular smooth muscle cell proliferation and inflammation, events leading to endothelial dysfunction, and atherosclerosis that are present in those destined for metabolic syndrome. In addition, the hypertensive phenotype that is a hallmark of metabolic syndrome may also be traced to blunted kidney development and renin-angiotensin system activation in growth-restricted offspring. The summative impact of these intrauterine programmed changes in terms of influencing adult health and disease encompasses dietary and lifestyle factors introduced postnatally. Establishing novel therapeutic interventions aimed at preventing and/or reducing in utero-induced insulin resistance and vascular dysfunction warrants investigation because the numbers of low birthweight babies continue to increase.

http://www.ncbi.nlm.nih.gov/pubmed/21710397

“Children’s high recall of food and beverage company sport sponsors and their positive attitudes towards these sponsors and their promotions is concerning as this is likely to be linked to children’s food preferences and consumption. **Limiting children’s exposure to this marketing is an important initiative to improve children’s nutrition.**”

International Journal Of Behavior, Nutrition And Physical Activity • September 2011

“Food company sponsors are kind, generous and cool”: (mis)conceptions of junior sports players

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Abstract

BACKGROUND

Children’s exposure to unhealthy food marketing influences their food knowledge, preferences and consumption. Sport sponsorship by food companies is widespread and industry investment in this marketing is increasing. This study aimed to assess children’s awareness of sport sponsors and their brand-related attitudes and purchasing intentions in response to this marketing.

METHODS

Sports clubs known to have food sponsors and representing the most popular sports for Australian children across a range of demographic areas were recruited. Interview-based questionnaires were conducted at clubs with children aged 10-14 years (n = 103) to examine their recall of local sports club and elite sport sponsors, and their attitudes towards sponsors and sponsorship activities.

RESULTS

Most children (68%) could recall sponsors of their sports club, naming a median of two sponsors, including a median of one food company sponsor each. Almost half (47%) of children could recall any sponsors of their favourite elite sporting team. Children aged 10-11 years were more likely than older children to report that they thought about sponsors when buying something to eat or drink ($P < 0.01$); that they liked to return the favour to sponsors by buying their products ($P < 0.01$); and that sponsors were ‘cool’ ($P = 0.02$). Most children had received a voucher or certificate from a food or beverage company to reward sport performance (86% and 76%, respectively). Around one-third of children reported liking the company more after receiving these rewards.

CONCLUSIONS

Children’s high recall of food and beverage company sport sponsors and their positive attitudes towards these sponsors and their promotions is concerning as this is likely to be linked to children’s food preferences and consumption. Limiting children’s exposure to this marketing is an important initiative to improve children’s nutrition.

Full text, graphs, charts and 26 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3179435/

Pathology & Biology (Paris) • June 2010

The health and technological implications of a better control of neoformed contaminants by the food industry

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Abstract

The recent discovery of the presence of variable amounts of the carcinogenic compound acrylamide in a wide range of severely heat-treated food products, such as fried potatoes, biscuits, bread and coffee or malt, as a result of the heat process, has induced an important research in the area of the Maillard reaction in food. The interaction between a specific food composition and the heat process applied results in the development of complex oxidation and glycation reactions, which give rise to a mixture of flavoured compounds and possible neoformed contaminants (NFC). Recommendations by the European Commission aim at monitoring the content of major NFC, such as acrylamide and furan, in a list of food products commercialized in Europe. On the other hand, the Commission for European Normalization (CEN) has created recently a new workgroup (WG13) responsible for normalization of analytical method for NFC assessment. The European collective research ICARE was carried out to identify the possible health consequences of the ingestion of heat-treated products, characterize the reaction kinetics leading to NFC and evaluate some mitigation procedures proposed by the CIAA toolbox, and finally develop a simple, rapid and non destructive control method based on fluorescence acquisition on the crushed food products and chemometric analysis of the spectral information. This paper summarizes the objectives and essential results obtained in the scope of the project, highlighting the need for evaluating the distribution of NFC in food products commercialized in Europe, as well as the impact of the food formula/recipe and process on Maillard derived NFC food levels. The potential of the Fluoralys sensor regarding its ability to control food contamination with NFC is presented. A decrease in NFC concentration of heat processed food should allow significantly limiting the exposure of populations to NFC and consequently the potential related health risk.

http://www.ncbi.nlm.nih.gov/pubmed/19906499

“Overall, the supermarket environment worsened due to an increase in cross-promotions targeted to children and adolescents and a decline in the nutritional quality of these products. This analysis failed to find improvements in food marketing to youth ...”

Public Health Nutrition • July 2010

Marketing foods to children and adolescents: licensed characters and other promotions on packaged foods in the supermarket

Author information

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Abstract

OBJECTIVE

To analyse cross-promotions targeted to children and adolescents on packaging in the supermarket.

DESIGN

On three occasions from 2006 to 2008, researchers purchased all foods in a large supermarket that included a cross-promotion on the package. A total of 397 products were categorized by promotional partner, food category, targeted age group, promotion type, product nutrition, and company policies on marketing to children.

RESULTS

The number of products with youth-oriented cross-promotions increased by 78 % during the period examined. Overall, 71 % of cross-promotions involved third-party licensed characters and 57 % appealed primarily to children under 12 years of age; however, the use of other forms of promotions increased from 5 % of the total in 2006 to 53 % in 2008, and promotions targeting pre-school and general audiences increased from 23 % to 54 % of the total. Only 18 % of products met accepted nutrition standards for foods sold to youth, and nutritional quality declined during the period examined. Food manufacturers with policies limiting marketing to children represented 65 % of all youth-oriented cross-promotions, their use of cross-promotions increased significantly, and the nutritional quality of their products did not improve. Some media companies did reduce the use of their properties on food promotions.

CONCLUSIONS

Overall, the supermarket environment worsened due to an increase in cross-promotions targeted to children and adolescents and a decline in the nutritional quality of these products. This analysis failed to find improvements in food marketing to youth and highlights the need to expand current industry self-regulatory pledges.

http://www.ncbi.nlm.nih.gov/pubmed/19719889

“Our data demonstrate that gut microbiota modulates hepatic gene expression and function by altering its xenobiotic response to drugs without direct contact with the liver.”

PLoS One • September 2009

Intestinal Microbiota Regulate Xenobiotic Metabolism in the Liver

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Abstract

Background

The liver is the central organ for xenobiotic metabolism (XM) and is regulated by nuclear receptors such as CAR and PXR, which control the metabolism of drugs. Here we report that gut microbiota influences liver gene expression and alters xenobiotic metabolism in animals exposed to barbiturates.

Principal findings

By comparing hepatic gene expression on microarrays from germfree (GF) and conventionally-raised mice (SPF), we identified a cluster of 112 differentially expressed target genes predominantly connected to xenobiotic metabolism and pathways inhibiting RXR function. These findings were functionally validated by exposing GF and SPF mice to pentobarbital which confirmed that xenobiotic metabolism in GF mice is significantly more efficient (shorter time of anesthesia) when compared to the SPF group.

Conclusion

Our data demonstrate that gut microbiota modulates hepatic gene expression and function by altering its xenobiotic response to drugs without direct contact with the liver.

Full text, graphs, charts and 38 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2734986/

Reproductive Toxicology • September 2009

Zebrafish embryos as models for embryotoxic and teratological effects of chemicals

Author information
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Abstract

“The experimental virtues of the zebrafish embryo such as small size, development outside of the mother, cheap maintenance of the adult made the zebrafish an excellent model for phenotypic genetic and more recently also chemical screens. The availability of a genome sequence and several thousand mutants and transgenic lines together with gene arrays and a broad spectrum of techniques to manipulate gene functions add further to the experimental strength of this model. Pioneering studies suggest that chemicals can have in many cases very similar toxicological and teratological effects in zebrafish embryos and humans. In certain areas such as cardiotoxicity, the zebrafish appears to outplay the traditional rodent models of toxicity testing. Several pilot projects used zebrafish embryos to identify new chemical entities with specific biological functions. In combination with the establishment of transgenic sensor lines and the further development of existing and new automated imaging systems, the zebrafish embryos could therefore be used as cost-effective and ethically acceptable animal models for drug screening as well as toxicity testing.”

http://www.ncbi.nlm.nih.gov/pubmed/19406227

National Review Of Microbiology • December 2009

What are the consequences of the disappearing human microbiota?

Author information

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Abstract

“Humans and our ancestors have evolved since the most ancient times with a commensal microbiota. The conservation of indicator species in a niche-specific manner across all of the studied human population groups suggests that the microbiota confer conserved benefits on humans. Nevertheless, certain of these organisms have pathogenic properties and, through medical practices and lifestyle changes, their prevalence in human populations is changing, often to an extreme degree. In this Essay, we propose that the disappearance of these ancestral indigenous organisms, which are intimately involved in human physiology, is not entirely beneficial and has consequences that might include post-modern conditions such as obesity and asthma.”

http://www.ncbi.nlm.nih.gov/pubmed/19898491

Annual Reviews Of Public Health • December 2009

A crisis in the marketplace: how food marketing contributes to childhood obesity and what can be done

Author information

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Abstract

“Reducing food marketing to children has been proposed as one means for addressing the global crisis of childhood obesity, but significant social, legal, financial, and public perception barriers stand in the way. The scientific literature documents that food marketing to children is (a) massive; (b) expanding in number of venues (product placements, video games, the Internet, cell phones, etc.); (c) composed almost entirely of messages for nutrient-poor, calorie-dense foods; (d) having harmful effects; and (e) increasingly global and hence difficult to regulate by individual countries. The food industry, governmental bodies, and advocacy groups have proposed a variety of plans for altering the marketing landscape. This article reviews existing knowledge of the impact of marketing and addresses the value of various legal, legislative, regulatory, and industry-based approaches to change.”

http://www.ncbi.nlm.nih.gov/pubmed/?term=18976142

Public Health And Nutrition • September 2008

The 'Sydney Principles' for reducing the commercial promotion of foods and beverages to children

Author information

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Abstract

A set of seven principles (the 'Sydney Principles') was developed by an International Obesity Taskforce (IOTF) Working Group to guide action on changing food and beverage marketing practices that target children. The aim of the present communication is to present the Sydney Principles and report on feedback received from a global consultation (November 2006 to April 2007) on the Principles. The Principles state that actions to reduce marketing to children should: (i) support the rights of children; (ii) afford substantial protection to children; (iii) be statutory in nature; (iv) take a wide definition of commercial promotions; (v) guarantee commercial-free childhood settings; (vi) include cross-border media; and (vii) be evaluated, monitored and enforced. The draft principles were widely disseminated and 220 responses were received from professional and scientific associations, consumer bodies, industry bodies, health professionals and others. There was virtually universal agreement on the need to have a set of principles to guide action in this contentious area of marketing to children. Apart from industry opposition to the third principle calling for a statutory approach and several comments about the implementation challenges, there was strong support for each of the Sydney Principles. Feedback on two specific issues of contention related to the age range to which restrictions should apply (most nominating age 16 or 18 years) and the types of products to be included (31% nominating all products, 24% all food and beverages, and 45% energy-dense, nutrient-poor foods and beverages). The Sydney Principles, which took a children's rights-based approach, should be used to benchmark action to reduce marketing to children. The age definition for a child and the types of products which should have marketing restrictions may better suit a risk-based approach at this stage. The Sydney Principles should guide the formation of an International Code on Food and Beverage Marketing to Children.

http://www.ncbi.nlm.nih.gov/pubmed/18510788

THE SEVEN WORLD HEALTH ORGANIZATION PRINCIPLES

The Principles state that actions to reduce marketing to children should:

(i) support the rights of children;

(ii) afford substantial protection to children;

(iii) be statutory in nature;

(iv) take a wide definition of commercial promotions;

(v) guarantee commercial-free childhood settings;

(vi) include cross-border media; and

(vii) be evaluated, monitored and enforced.

Journal Of The American Dieticians Association • April 2008

Nine out of 10 food advertisements shown during Saturday morning children's television programming are for foods high in fat, sodium, or added sugars, or low in nutrients

Author information

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Abstract

A 2005 review by the Institute of Medicine of the National Academies concluded that food marketing influences children's food preferences, consumption, and health. Given the powerful influence of marketing on children's diets, this cross-sectional study examined the types of foods, the nutritional quality of those foods, and the marketing techniques and messages used in food advertising during Saturday morning children's television programming. During 27.5 hours of programming in May 2005, 49% of advertisements shown were for food (281 food advertisements out of 572 total advertisements). The most commonly advertised food categories were ready-to-eat breakfast cereal and cereal bars (27% of all food advertisements), restaurants (19% of food advertisements), and snack foods (18% of food advertisements). Ninety-one percent of food advertisements were for foods or beverages high in fat, sodium, or added sugars or were low in nutrients. Cartoon characters were used in 74% of food advertisements, and toy or other giveaways were used in 26% of food advertisements. About half of food advertisements contained health/nutrition or physical activity messages and 86% of food advertisements contained emotional appeals. This study provides food and nutrition professionals with information about the amount and types of food children are encouraged to eat during Saturday morning television programming. The findings can help food and nutrition professionals counsel children about healthful eating and/or develop programs or policies to balance those advertisements with healthful eating messages.

http://www.ncbi.nlm.nih.gov/pubmed/18375225

Future Child • Spring 2008

Children as consumers: advertising and marketing

By SL Calvert
Department of Psychology, Georgetown University, USA

Abstract

“Marketing and advertising support the U.S. economy by promoting the sale of goods and services to consumers, both adults and children. Sandra Calvert addresses product marketing to children and shows that although marketers have targeted children for decades, two recent trends have increased their interest in child consumers. First, both the discretionary income of children and their power to influence parent purchases have increased over time. Second, as the enormous increase in the number of available television channels has led to smaller audiences for each channel, digital interactive technologies have simultaneously opened new routes to narrow cast to children, thereby creating a growing media space just for children and children’s products. Calvert explains that paid advertising to children primarily involves television spots that feature toys and food products, most of which are high in fat and sugar and low in nutritional value. Newer marketing approaches have led to online advertising and to so-called stealth marketing techniques, such as embedding products in the program content in films, online, and in video games. All these marketing strategies, says Calvert, make children younger than eight especially vulnerable because they lack the cognitive skills to understand the persuasive intent of television and online advertisements. The new stealth techniques can also undermine the consumer defenses even of older children and adolescents. Calvert explains that government regulations implemented by the Federal Communications Commission and the Federal Trade Commission provide some protection for children from advertising and marketing practices. Regulators exert more control over content on scarce television airwaves that belong to the public than over content on the more open online spaces. Overall, Calvert concludes, children live and grow up in a highly sophisticated marketing environment that influences their preferences and behaviors.”

http://www.ncbi.nlm.nih.gov/pubmed/21338011

Obesity Reviews • July 2008

Assessing ‘fun foods’: nutritional content and analysis of supermarket foods targeted at children

By C. Elliott

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Abstract

“This article provides a nutritional profile of foods targeted specifically at children in the Canadian supermarket. Excluding confectionery, soft drinks and bakery items, 367 products were assessed for their nutritional composition. The article examines the relationship between ‘fun food’ images/messages, product claims and actual product nutrition. Among other findings, it concludes that approximately 89% of the products analysed could be classified as of poor nutritional quality owing to high levels of sugar, fat and/or sodium. Policy considerations need to be made in light of the fact that ‘fun food’ is a unique category that poses special challenges; as such, recommendations regarding food labelling and packaging are presented.”

http://www.ncbi.nlm.nih.gov/pubmed/17961131

Health Promotion International • December 2008

Persuasive food marketing to children: use of cartoons and competitions in Australian commercial television advertisements

Author information
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Abstract

“While there is a recognized link between high levels of exposure to advertising of unhealthy foods and overweight and obesity among children, there is little research on the extent to which these exposures include persuasive marketing techniques. This study aimed to measure children’s exposure to the use of persuasive marketing within television food advertisements. Advertisements broadcast on all three commercial Australian television channels were recorded for an equivalent 1 week period in May 2006 and 2007 (714 h). Food advertisements were analysed for their use of persuasive marketing, including premium offers, such as competitions, and the use of promotional characters, including celebrities and cartoon characters. Advertised foods were categorized as core, non-core or miscellaneous foods. Commercial data were purchased to determine children’s peak viewing times and popular programs. A total of 20,201 advertisements were recorded, 25.5% of which were for food. Significantly more food advertisements broadcast during children’s peak viewing times, compared to non-peak times, contained promotional characters ($P < 0.05$) and premium offers ($P < 0.001$). During programs most popular with children, there were 3.3 non-core food advertisements per hour containing premium offers, compared to 0.2 per hour during programs most popular with adults. The majority of advertisements containing persuasive marketing during all viewing periods were for non-core foods. Persuasive marketing techniques are frequently used to advertise non-core foods to children, to promote children’s brand recognition and preference for advertised products. Future debate relating to television advertising regulations must consider the need to restrict the use of persuasive marketing techniques to children.”

Full text, graphs, charts and 15 references

http://heapro.oxfordjournals.org/content/23/4/337.long

“Through its food marketing, the Nickelodeon entertainment company influences the diets of millions of American children. Unfortunately, eight of ten foods, beverages, and restaurant meals advertised on Nickelodeon’s television station, in its magazine, or tied to its characters are of poor nutritional quality.”

American Journal Of Preventive Medicine • July 2007

Nickelodeon markets nutrition-poor foods to children

Author information

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Abstract

BACKGROUND

While many factors contribute to childhood obesity and children’s poor diets, food marketing affects children’s food choices, preferences, their diets, and their health. The purpose of this study was to assess the nutritional quality of the foods marketed by one of the largest companies that markets food to children, Nickelodeon.

METHODS

In fall 2005, the nutritional quality of foods advertised via Nickelodeon media and with Nickelodeon characters was assessed. The cross-sectional sample included food ads on the Nickelodeon television station and in Nickelodeon magazine, product packages with Nickelodeon characters found in one large urban grocery store, and meals at restaurants with promotions tied to Nickelodeon programs or characters.

RESULTS

Of 168 television food ads, 148 (88%) were for foods of poor nutritional quality. Of 21 magazine food ads, 16 (76%) were for foods of poor nutritional quality. Fifteen grocery store products were identified with Nickelodeon characters on the packaging; nine (60%) were foods of poor nutritional quality. In addition, of the 48 possible children’s meal combinations at restaurants with promotional offers tied to Nickelodeon programs, 45 (94%) were of poor nutritional quality.

CONCLUSIONS

Through its food marketing, the Nickelodeon entertainment company influences the diets of millions of American children. Unfortunately, eight of ten foods, beverages, and restaurant meals advertised on Nickelodeon’s television station, in its magazine, or tied to its characters are of poor nutritional quality. Rather than undermining parents’ efforts to feed their children healthfully, Nickelodeon should support parents by setting nutrition standards and marketing to children only foods that meet those standards.

http://www.ncbi.nlm.nih.gov/pubmed/17572311

“... plant polyphenols play a significant inhibitory role on Benzene-induced mutagenicity.”

Food Chemistry And Toxicology • October 2007

Effects of various plant polyphenols on bladder carcinogen benzidine-induced mutagenicity

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Abstract

Benzidine (Bz), a human bladder carcinogen, was strongly mutagenic to Salmonella TA102 tester strain in the Ames Salmonella microsome/mutagenicity assay in the presence of rat liver S9 mix. Various non-mutagenic plant polyphenols were included in the assay to test their inhibitory effects on the Bz-induced mutations. Coumestrol, ellagic acid (EA), (-)-epicatechin (EC), (-)-epichatechingallate (ECG), gallic acid (GA), (-)-gallocatechin (GC), plumbagin, propyl gallate (PG), taxifolin, and 2,2’,4’-trihydroxychalcone were found to have a strong inhibitory effect on Bz-induced mutations. (-)-Epigallo-catechingallate (EGCG), fisetin, (-)-gallocatechingallate (GCG), and piceatannol were moderately inhibitory to the mutations; whereas, (-)-catechin, (-)-catechingallate (CG), and reseveratrol were weakly inhibitory to the mutations. (-)-Epigallocatechin (EGC) and 7,3’,4’-trihydroxy isoflavon were not inhibitory to the Bz-induced mutations. Isoliquirtigenin, quercetin dihydrate, and rhein were found to be mutagenic in tester strain TA102. Benzidine mediated lipid peroxidation was conducted employing the thiobarbituric acid reactive substances (TBARS) assay using linoleic acid as a substrate. In the presence of rat liver S9 mix, Bz could cause lipid peroxidation as an outcome of production of oxygen free radicals. Incorporation of the above mentioned non-mutagenic plant polyphenols significantly inhibited benzidine mediated lipid peroxidation in a time dependent manner. These polyphenols also effectively reduced the iron mediated lipid peroxidation. Thus, it is concluded that the inhibition of oxidative mutagenicity of Bz by plant polyphenols could be due to an inhibitory effect of plant polyphenols on the bioactivating enzymes such as cytochrome P-450 and peroxidase and the chelation of iron present in the cytochrome P-450 in the S9 mix. Thus, these plant polyphenols play a significant inhibitory role on Bz-induced mutagenicity.

http://www.ncbi.nlm.nih.gov/pubmed/17560706

Social Science And Medicine • October 2007

The effects of television advertisements for junk food versus nutritious food on children's food attitudes and preferences

Author information

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Abstract

"Television (TV) food advertising has attracted criticism for its potential role in promoting unhealthy dietary practices among children. Content analyses indicate junk food advertising is prevalent on Australian children's TV; healthy eating is rarely promoted. This paper presents (a) a cross-sectional survey examining associations between children's regular TV viewing habits and their food-related attitudes and behaviour; and (b) an experiment assessing the impact of varying combinations of TV advertisements (ads) for unhealthy and healthy foods on children's dietary knowledge, attitudes and intentions. The experimental conditions simulated possible models for regulating food ads on children's TV. Participants were 919 grade five and six students from schools in Melbourne, Australia. The survey showed that heavier TV use and more frequent commercial TV viewing were independently associated with more positive attitudes toward junk food; heavier TV use was also independently associated with higher reported junk food consumption. The experiment found that ads for nutritious foods promote selected positive attitudes and beliefs concerning these foods. Findings are discussed in light of methodological issues in media effects research and their implications for policy and practice. It is concluded that changing the food advertising environment on children's TV to one where nutritious foods are promoted and junk foods are relatively unrepresented would help to normalize and reinforce healthy eating."

http://www.ncbi.nlm.nih.gov/pubmed/17587474

Archives In Toxicology • October 2007

Renal deterioration caused by carcinogens as a consequence of free radical mediated tissue damage: a review of the protective action of melatonin

Author information

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Abstract

“This brief review summarizes some of the publications that document the preventive role of melatonin in kidney damage caused by carcinogens such as 2-nitropropane, arsenic, carbon tetrachloride, nitrilotriacetic acid and **potassium bromate.** Numerous chemicals generate excessive free radicals that eventually induce renal worsening. Melatonin partially or totally prevents free radical mediated tissue damages induced by many carcinogens. Protective actions of melatonin against the harmful effects of carcinogens are believed to stem from its direct free radical scavenging and indirect antioxidant activities. Dietary or pharmacologically given melatonin may attenuate the oxidative stress, thereby mitigating the subsequent renal damage.”

http://www.ncbi.nlm.nih.gov/pubmed/17823789

The Journal Of Adhesive Dentistry • Spring 2005

Effect of ozone on enamel and dentin bond strength

Author information

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Abstract

PURPOSE

To evaluate the influence of direct high-dose gaseous ozone application (2100 ppm) on dentin and enamel shear bond strength.

MATERIALS AND METHODS

Ten bovine enamel and dentin samples per group were pretreated as follows: (I) ozone application (Healozone, KaVo) for 60 s alone or (II) with subsequent application of a fluoride- and xylitol-containing antioxidant (liquid reductant), (III) light-activated bleaching with 35% hydrogen peroxide for 5 min serving as negative control (Hi-Lite, Shofu), and (IV) untreated enamel and dentin (positive control). Specimens were bonded with a functional 3-step adhesive system (Syntac Classic, Ivoclar Vivadent) and restored with a composite (Tetric Ceram, Ivoclar Vivadent) according to the Ultradent method. After storage in water at 37 degrees C for 24 h, shear bond strength was measured using a Zwick universal testing machine. Data were analyzed using ANOVA and Scheffe's post hoc analysis.

RESULTS

In concordance with the existing literature, bleaching resulted in significantly decreased bond strength ($p < 0.05$) on enamel specimens. No decrease in shear bond strength was detected for ozone-pretreated specimens compared to untreated controls.

CONCLUSION

Despite a possible retention of surface and subsurface oxide-related substances during high-dose ozone application, shear bond strength was not impaired. Thus, adhesive restoration placement should be possible immediately after ozone application for cavity disinfection.

http://www.ncbi.nlm.nih.gov/pubmed/15892361

The Journal Of Exposure Analysis And Environmental Epidemiology • July 2005

Exposures of preschool children to chlorpyrifos and its degradation product 3,5,6-trichloro-2-pyridinol in their everyday environments

Author information

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> “In conclusion, the results showed that the preschool children were exposed to chlorpyrifos and 3,5,6-trichloro-2-pyridinol (TCP) from several sources, through several pathways and routes.”

Abstract

As part of the Children’s Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) study, we investigated the exposures of preschool children to chlorpyrifos and its degradation product 3,5,6-trichloro-2-pyridinol (TCP) in their everyday environments. During this study, the participants were still able to purchase and apply chlorpyrifos at their homes or day care centers. Participants were recruited randomly from 129 homes and 13 day care centers in six North Carolina counties. Monitoring was performed over a 48-h period at the children’s homes and/or day care centers. Samples that were collected included duplicate plate, indoor and outdoor air, urine, indoor floor dust, play area soil, transferable residues (PUF roller), and surface wipes (hand, food preparation, and hard floor). The samples were extracted and analyzed by gas chromatography/mass spectrometry. Chlorpyrifos was detected in 100% of the indoor air and indoor floor dust samples from homes and day care centers. TCP was detected at homes and day care centers in 100% of the indoor floor dust and hard floor surface wipe, in >97% of the solid food, and in >95% of the indoor air samples. Generally, median levels of chlorpyrifos were higher than those of TCP in all media, except for solid food samples. For these samples, the median TCP concentrations were 12 and 29 times higher than the chlorpyrifos concentrations at homes and day care centers, respectively. The median urinary TCP concentration for the preschool children was 5.3 ng/ml and the maximum value was 104 ng/ml. The median potential aggregate absorbed dose (ng/kg/day) of chlorpyrifos for these preschool children was estimated to be 3 ng/kg/day. The primary route of exposure to chlorpyrifos was through dietary intake, followed by inhalation. The median potential aggregate absorbed dose of TCP for these children was estimated to be 38 ng/kg/day, and dietary intake was the primary route of exposure. The median excreted amount of urinary TCP for these children was estimated to be 117 ng/kg/day. A full regression model of the relationships among chlorpyrifos and TCP for the children in the home group explained 23% of the variability of the urinary TCP concentrations by the three routes of exposure (inhalation, ingestion, dermal absorption) to chlorpyrifos and TCP. However, a final reduced model via step-wise regression retained only chlorpyrifos through the inhalation route and explained 22% of the variability of TCP in the children’s urine. The estimated potential aggregate absorbed doses of chlorpyrifos through the inhalation route were low (median value, 0.8 ng/kg/day) and could not explain most of the excreted amounts of urinary TCP. This suggested that there were other possible sources and pathways of exposure that contributed to the estimated potential aggregate absorbed doses of these children to chlorpyrifos and TCP. One possible pathway of exposure that was not accounted for fully is through the children’s potential contacts with contaminated surfaces at homes and day care centers. In addition, other pesticides such as chlorpyrifos-methyl may have also contributed to the levels of TCP in the urine. Future studies should include additional surface measurements in their estimation of potential absorbed doses of preschool children to environmental pollutants. In conclusion, the results showed that the preschool children were exposed to chlorpyrifos and TCP from several sources, through several pathways and routes.

Full text, graphs, charts and 20 references

http://www.nature.com/jes/journal/v15/n4/full/7500406a.html

Food Safety Commission • July 2005

Evaluation Report of Food Additives Acetaldehyde

Original Japanese Provisional Translation

Abstract

Introduction

Acetaldehyde has a fruity aroma, and is naturally contained in foods such as fruits and fruit juice (0.2-230 ppm), vegetables (0.2-400 ppm), dairy products (0.001-76 ppm) and bread (4.2-9.9 ppm) 1), 2). In addition, acetaldehyde is contained in beverages such as tea and soft drinks (0.2-0.6 ppm), beer (0.6-24 ppm), wine (0.7-290 ppm) and spirits (0.5-104 ppm) 2). In Europe and the United States, it is added to reproduce flavors in various processed foods such as soft drinks (average usage: 5.05 ppm) and candy (average usage: hard type: 9.29 ppm, soft type 3.26 ppm) 3).

Evaluation And Results

High-dose inhalation exposure of acetaldehyde has carcinogenicity. A negative result was obtained in an Ames test, while positive results were obtained in other genotoxicity tests. Therefore, this substance is considered to have qualitative genotoxicity, but quantitative evaluation will be needed in the future. Test data on genotoxicity in cancer-target organs has not been obtained. In addition, the estimated intake of this substance exceeded the acceptable intake of class I substances, and the safety margin based on the 11-week repeated-dose toxicity study is below the appropriate safety margin (1,000).

However, the dose in the inhalation test is at a higher level than that of the estimated exposure in humans, thus, the observed carcinogenesis was presumed to have resulted from the direct exposure to highly cytotoxic acetaldehyde. This substance is consumed from daily foods such as fruit and alcoholic beverages, and the volume of intake is supposed to be larger than that being consumed as flavoring agent.

The volume presumed to be consumed from food is metabolized by aldehyde dehydrogenase (ALDH) in the gastrointestinal mucosa and eliminated after binding with proteins. In addition, the majority is metabolized by the first pass effect in the liver even if absorbed from the gastrointestinal tract. Therefore, a limited amount is believed to enter the systemically-circulating blood.

This substance is a biogenic substance, used for a long time in the U.S. and Europe, and no health hazards have been reported due to its use as a flavor. According to the evaluation carried out by the JECFA, the substance is classified into class I, and the estimated intake exceeds the acceptable intake of class I, however, this substance is free of safety problems as a flavoring agent because it is presumed to be metabolized completely into biogenic substances and its level do not exceed the physiological range.

Full text, graph and 28 references

https://www.fsc.go.jp/english/evaluationreports/foodadditive/acetaldehyde_report.pdf

Obesity Review • August 2005

Evidence of a possible link between obesogenic food advertising and child overweight

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Abstract

“A recent review of the literature concluded that advertising of foods on television may influence children’s food choices and encourage unhealthy diets, but the review acknowledged there was a lack of clear evidence in coming to this conclusion. The present paper examines ecological evidence for a link between advertising to children and the risk of overweight using data from surveys of advertising on children’s television and estimates of the prevalence of overweight among children, in the USA, Australia and eight European countries. A significant association was found between the proportion of children overweight and the numbers of advertisements per hour on children’s television, especially those advertisements that encourage the consumption of energy-dense, micronutrient-poor foods ($r = 0.81$, $P < 0.005$). A weaker, negative association was found between the proportion of children overweight and the number of advertisements encouraging healthier diets ($r = -0.56$, $P < 0.10$). The quantity of advertising on children’s television appears to be related to the prevalence of excess body weight among children. Furthermore, the content of the advertising appears to have a specific effect. The findings justify the need for taking precautionary measures to reduce children’s exposure to obesogenic marketing practices.”

http://www.ncbi.nlm.nih.gov/pubmed/16045635

Pediatric Allergy And Immunology • June 2004

Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention

By S. Halken

Abstract

The development and phenotypic expression of atopic diseases depends on a complex interaction between genetic factors, environmental exposure to allergens,and non-specific adjuvant factors, such as tobacco smoke, air pollution and infections. Preventive measures may include both exposure to allergens and adjuvant risk/protective factors and pharmacological treatment. These measures may address the general population, children at risk for development of atopic disease (high-risk infants), children with early symptoms of allergic disease or children with chronic disease. The objective for this review was to evaluate possible preventive measures as regards prevention of development of allergic disease in childhood--primary prevention--and also some aspects of the effect of specific allergy treatment as regards secondary prevention in children with allergic asthma and allergic rhinoconjunctivitis. In one prospective observational study of a birth cohort of unselected infants we evaluated possible predictive/risk factors. In two prospective intervention studies including 1 yr birth cohorts of high-risk(HR) infants we investigated the effect of feeding HR infants exclusively breast milk (BM) and/or hydrolyzed cow's milk-based formula the first 4-6 months as regards: (i) the allergy preventive effect of BM/extensively hydrolysed formula (eHF) compared with ordinary cow's milk-based formula, (ii) the effect of two different eHFs, a whey (Profylac) and a casein-based (Nutramigen) formula, as regards development of cow's milk protein allergy (CMA), and (iii) a comparison of the preventive effect of eHF (Profylac/Nutramigen) with a partially hydrolyzed cow's milk-based formula (pHF) (NanHA) as regards development of CMA. None of the mothers had a restricted diet during pregnancy or lactation period. In two prospective randomized intervention studies we evaluated the preventive effect of specific allergen avoidance and specific immunotherapy (SIT) in children with allergic asthma and allergic rhinoconjunctivitis, respectively. The combination of atopic heredity and elevated cord blood IgE resulted in the best predictive discrimination as regards development of allergic disease. The optimal high-risk group was defined by either double parental atopic predisposition or single atopic predisposition, the latter combined with a cord blood IgE > or = 0.3 kU/1. 66% of unselected infants were daily exposed to tobacco smoke, which was a significant risk factor for recurrent wheezing until the age of 1.5 yr. HR infants were breastfed for a longer period and less exposed to tobacco smoke than unselected infants. Exclusively BM/eHF for at least 4 months was associated with a significantly reduced cumulative prevalence of CMA [3.6% (5/141) vs. 20%(15/75) in the control group] up to 5 yr. The effect of the two different eHFs was similar. Exclusively breastfed infants were significantly less exposed to tobacco smoke and pets, had solid foods introduced later and belonged to higher social classes. pHF was significantly (p = 0.05) less effective than eHF as regards prevention of development of CMA. A diet period of 4 months seems to be as efficient as 6 months or more as regards development of CMA. A few ongoing prospective, randomized intervention studies have produced the first indication that avoidance of indoor allergens such as house dust mite (HDM) in HR infants may reduce the incidence of severe wheeze and sensitization during the first 1-4 yr of age. Long-term follow-up is awaited. In a prospective, double-blind placebo-controlled study in children with doctors diagnosed asthma and documented HDM allergy, we found that semi-permeable polyurethane mattress and pillow encasings (Allergy Control) when compared with placebo encasings resulted in a significant perennial reduction of HDM exposure and a significant reduction in the needed dose of inhaled steroids by approximately 50% (mean dose: 408 microg--227 microg/day) after 1-yr follow-up. In another randomized prospective study we investigated the possible preventive effect of SIT in children with allergic rhinoconjunctivitis and grass/birch pollen allergy as regards development of asthma. Among those without asthma significantly fewer in the SIT group developed asthma when compared with the control group (19/79 = 24% vs.32/72 = 44%) after the first 3 yr; and methacholinebronchial provocation test results improved significant in the SIT group. The results of our studies support the evidence that the risk for development of early allergic manifestations e.g. CMA and atopic dermatitis can be reduced significantly by simple dietary measures for the first4 months of life. In all infants breastfeeding should beencouraged for at least 4-6 months, and exposure to tobacco smoke should be avoided during pregnancy and early childhood. In HR infants a documented hypoallergenic formula (at present eHF) is recommended if exclusive breastfeeding is not possible for the first 4 months. In homes of HR-infants, current evidence supports measures to reduce the levels of indoor allergens. e.g. HDM and pets. In symptomatic children allergen-specific treatment may influence both the symptoms and the prognosis. Allergen avoidance can reduce the need for pharmacological treatment, SIT may have the potential for preventing the development of asthma in children with allergic rhinoconjunctivitis. and it may be possible to interfere with the natural course of allergic diseases.

http://www.ncbi.nlm.nih.gov/pubmed/15125698

“A fermented formula may reduce the severity of acute diarrhea among healthy young infants. This outcome may be linked to the bifidogenic effects of fermentation products and their interactions with the intestinal immune system.”

Journal Of Pediatrics, Gastroenterology And Nutrition • August 2004

Effects of long-term consumption of a fermented infant formula (with Bifidobacterium breve c50 and Streptococcus thermophilus 065) on acute diarrhea in healthy infants

Thibault H1, Aubert-Jacquin C, Goulet O.

Author information

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Abstract

OBJECTIVE

To determine whether long-term consumption of a fermented infant formula could influence the incidence of acute diarrhea and its severity in healthy infants.

METHOD

Nine hundred seventy-one infants, ranging in age from 4 to 6 months, were included in a randomized, double-blind, placebo-controlled trial during a period of 5 months. They consumed daily either a fermented infant formula (FF) (fermentation with Bifidobacterium breve C50 and Streptococcus thermophilus 065) or a standard infant formula (SF) of the same nutritional composition.

EVALUATION CRITERIA

Number and duration of acute diarrhea episodes were evaluated. Severity of the episodes was determined by the number of hospital admissions, incidence of dehydration, number of medical consultations, number of oral rehydration solution prescriptions, and number of formula switches.

RESULTS

Growth of the infants and acceptability of the formulas were identical in the two groups. Incidence, duration of diarrhea episodes, and number of hospital admissions did not differ significantly between groups. Episodes were less severe in the FF (fermented formula) group. There were fewer cases of dehydration 2.5%versus 6.1% (P = 0.01), fewer medical consultations (46%v 56.6%, P = 0.003), fewer ORS prescriptions 41.9%v 51.9% (P = 0.003) and fewer switches to other formulas (59.5%v 74.9%, P = 0.0001) in FF infants compared to SF.

CONCLUSION

A fermented formula may reduce the severity of acute diarrhea among healthy young infants. This outcome may be linked to the bifidogenic effects of fermentation products and their interactions with the intestinal immune system.

http://www.ncbi.nlm.nih.gov/pubmed/15269618

“**Of all the additives, dyes were the most genotoxic**. Amaranth, Allura Red, New Coccine, Tartrazine, Erythrosine, Phloxine, and Rose Bengal induced dose-related DNA damage in the glandular stomach, colon, and/or urinary bladder. **All seven dyes induced DNA damage in the gastrointestinal organs at a low dose** (10 or 100mg/kg). Among them, Amaranth, Allura Red, New Coccine, and Tartrazine induced DNA damage in the colon at close to the acceptable daily intakes (ADIs). Two antioxidants (butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)), three fungicides (biphenyl, sodium o-phenylphenol, and thiabendazole), and four sweeteners—sodium cyclamate, saccharin, sodium saccharin, and sucralose—also induced DNA damage in gastrointestinal organs.”

Mutation Research • August 2002

The comet assay with 8 mouse organs: results with 39 currently used food additives

Author information
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Abstract

We determined the genotoxicity of 39 chemicals currently in use as food additives. They fell into six categories-dyes, color fixatives and preservatives, preservatives, antioxidants, fungicides, and sweeteners. We tested groups of four male ddY mice once orally with each additive at up to 0.5xLD(50) or the limit dose (2000mg/kg) and performed the comet assay on the glandular stomach, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow 3 and 24h after treatment. Of all the additives, dyes were the most genotoxic. Amaranth, Allura Red, New Coccine, Tartrazine, Erythrosine, Phloxine, and Rose Bengal induced dose-related DNA damage in the glandular stomach, colon, and/or urinary bladder. All seven dyes induced DNA damage in the gastrointestinal organs at a low dose (10 or 100mg/kg). Among them, Amaranth, Allura Red, New Coccine, and Tartrazine induced DNA damage in the colon at close to the acceptable daily intakes (ADIs). Two antioxidants (butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)), three fungicides (biphenyl, sodium o-phenylphenol, and thiabendazole), and four sweeteners (sodium cyclamate, saccharin, sodium saccharin, and sucralose) also induced DNA damage in gastrointestinal organs. Based on these results, we believe that more extensive assessment of food additives in current use is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/12160896

Minerva Pediatrics • October 2002

Television and children's consumption patterns: A review of the literature

Author information

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Abstract

"The recent increase in childhood obesity has, among other things, focused attention on the role that television may play. This paper summarizes results of studies published in peer review journals since 1970 with data pertaining to the relationship between television use and children's food intake. Studies fall into four categories: content analyses; effects of television advertising on children's food behaviors; television and pediatric obesity, with effects on children's dietary intake and physical activity; and television use and children's food consumption patterns. Content analyses have shown that food is the most frequently advertised product category on children's TV. The majority of these ads target highly sweetened products, but more recently, the proportion from fast food meal promotions has been growing. Controlled studies on children's choices have consistently shown that children exposed to advertising choose advertised food products at significantly higher rates than do those not exposed. Purchase request studies have documented associations between number of hours of TV watched and number of requests from the child to the mother for specific food items, as well as the presence of those items in the home. Greater TV use has been associated with higher intakes of energy, fat, sweet and salty snacks, and carbonated beverages and lower intakes of fruit and vegetables. Several large studies have documented associations between number of hours of TV watched and both the prevalence and incidence of obesity. The combination of lifestyle factors that accompany heavy television use appear to place children at risk of obesity and poor nutritional status."

http://www.ncbi.nlm.nih.gov/pubmed/12244280

American Journal Of Clinical Nutrition • November 2002

Inverse association between the effect of carbohydrates on blood glucose and subsequent short-term food intake in young men

Author information

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Abstract

BACKGROUND

A primary mechanism by which carbohydrates are thought to regulate satiety and food intake is through their effect on blood glucose.

OBJECTIVES

The objectives were to describe the effect of defined carbohydrate preloads on food intake and blood glucose and to determine the association between food intake and blood glucose.

DESIGN

Three experiments were conducted in which selected carbohydrates as 1255-kJ isovolumetric beverages were administered to young men after an overnight fast. Measurements of blood glucose and appetite were made at specified times during the next 60 min. Food intake was measured at 60 min.

RESULTS

Glucose resulted in the highest glycemic response, which was followed, in order, by the responses to polycose, sucrose, amylopectin, a fructose-glucose mixture, and amylose. The high-glycemic-index preloads (glucose, polycose, and sucrose) resulted in lower mealtime energy intake during a test meal at 1 h, but the low-glycemic-index preloads (amylose, amylopectin, and a fructose-glucose mixture) did not. An inverse relation was observed between the blood glucose concentrations in the area under the curve and the subjective appetite ($r = -0.23$, $P < 0.05$) and food intake at 60 min ($r = -0.24$, $P < 0.05$).

CONCLUSIONS

Food intake and subjective appetite are inversely associated with blood glucose response in the 60 min after consumption of carbohydrates. Carbohydrates with a high glycemic index (glucose, polycose, and sucrose) suppress subjective appetite and food intake in the short term, but those with a low glycemic index (amylose and amylopectin) do not.

Full text, graphs, charts and 38 references

http://ajcn.nutrition.org/content/76/5/1023.long

Reviews In Environmental Contamination And Toxicology • December 2002

Pollutants in house dust as indicators of indoor contamination

Author information

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Abstract

This review summarizes occurrence of organic and inorganic contaminants in house dust and the contribution of house dust as a marker of indoor exposure. Several studies have identified house dust as an important route of toxicant exposure. Often levels of pollutants found in house dust, including compounds banned long ago, are significant sources of exposure for the general population, especially children. House dust is a sink and repository for semivolatile organic compounds and particle-bound matter. Analyses of compounds in house dust are a measure of indoor contamination but may also provide valuable information for assessment of human indoor exposure. The objective of analyzing house dust are to describe the extent, distribution, and determinants of exposure, to identify possible sources of indoor contamination, or to record elevated indoor exposure leading to intervention or sanitation. House dust and compounds adsorbed to house dust may enter the human body by inhalation of suspended and resuspended particles, through nondietary ingestion of dust, through ingestion of particles adhering to food, surfaces in the homes, and on the skin as well as by absorption through the skin. The quantity of dust inhaled and deposited in the differing parts of the alveolar tract is dependent on the aerodynamic diameter. Exposure to house dust does not exclusively and may not even predominantly occur via inhalation, however. For instance, ingestion of house dust particles adhering to food, objects, and the skin or direct absorption through the skin may be primary routes of exposure (Lewis et al. 1994). Samples referred to as “house dust” vary significantly because house dust may be of different origin, amount, and composition and the method of sampling the dust influences the properties of the sample used for analysis. Passive and active sampling methods are described and discussed. For the analysis of organic pollutants in house dust, the < or = 63-microns fraction should be favored because variances caused by inhomogeneity of the subsample are low. Results from studies on house dust are presented for polychlorinated biphenyls (PCB), polycyclic aromatic hydrocarbons (PAH), plasticizers (phthalates, phenols), flame retardants, other organic xenobiotics, and inorganic constituents. If available, medians as a measure of the average concentration and the 90th or 95th percentiles are added as reference values. The review of the literature points out that ingestion of house dust may be a major route of exposure to pesticides for infants and toddlers. So far, only a few guideline values or limiting values for house dust exist. For lead in house dust, the health risk is regulated only in the U.S. and for PAH in the Federal Republic of Germany. Risk associated with the ingestion of contaminated dust by small children (age, 1-6 years; mean body weight, 16 kg) can be estimated using the chronic oral reference dose (RfD) and a daily intake of 100 mg house dust. The tentative benchmark house dust concentrations that are believed to be without health effect for small children were calculated for several compounds from their current RfD. Comparison with the maximum concentrations reviewed for chlorpyrifos, DDT, and diazinon indicates that the tolerable exposure concentration in house dust might be exceeded and that chlorpyrifos especially can be considered as a potential hazard to householders. The role of house dust as an exposure source is gaining more attention over the years but several open questions related to health remain to be resolved. Pesticides applied outside or within the household that are absorbed and preserved by house dust can lead through the everyday activities of children and infants to increased exposure. Residential exposure including house dust residues contribute to combined exposure from dietary and nondietary sources. It is justified to shift more attention to indoor pollution by house dust contamination and to improve the risk assessment of nondietary ingestion, but any health-based standard must be accompanied by a specific dust sampling method.

http://www.ncbi.nlm.nih.gov/pubmed/12206053

Journal Of Pineal Research • January 1995

A review of the evidence supporting melatonin's role as an antioxidant

Author information

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Barlow-Walden L, Chuang J, Ortiz GG, Acuña-Castroviejo D.

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Abstract

This survey summarizes the findings, accumulated within the last 2 years, concerning melatonin's role in defending against toxic free radicals. Free radicals are chemical constituents that have an unpaired electron in their outer orbital and, because of this feature, are highly reactive. Inspired oxygen, which sustains life, also is harmful because up to 5% of the oxygen (O2) taken in is converted to oxygen-free radicals. The addition of a single electron to O2 produces the superoxide anion radical (O2-.); O2-. is catalytic-reduced by superoxide dismutase, to hydrogen peroxide (H2O2). Although H2O2 is not itself a free radical, it can be toxic at high concentrations and, more importantly, it can be reduced to the hydroxyl radical (.OH). The .OH is the most toxic of the oxygen-based radicals and it wreaks havoc within cells, particularly with macromolecules. In recent in vitro studies, melatonin was shown to be a very efficient neutralizer of the .OH; indeed, in the system used to test its free radical scavenging ability it was found to be significantly more effective than the well known antioxidant, glutathione (GSH), in doing so. Likewise, melatonin has been shown to stimulate glutathione peroxidase (GSH-Px) activity in neural tissue; GSH-PX metabolizes reduced glutathione to its oxidized form and in doing so it converts H2O2 to H2O, thereby reducing generation of the .OH by eliminating its precursor. More recent studies have shown that melatonin is also a more efficient scavenger of the peroxyl radical than is vitamin E. The peroxyl radical is generated during lipid peroxidation and propagates the chain reaction that leads to massive lipid destruction in cell membranes. In vivo studies have demonstrated that melatonin is remarkably potent in protecting against free radical damage induced by a variety of means. Thus, DNA damage resulting from either the exposure of animals to the chemical carcinogen safrole or to ionizing radiation is markedly reduced when melatonin is co-administered. Likewise, the induction of cataracts, generally accepted as being a consequence of free radical attack on lenticular macromolecules, in newborn rats injected with a GSH-depleting drug are prevented when the animals are given daily melatonin injections. Also, paraquat-induced lipid peroxidation in the lungs of rats is overcome when they also receive melatonin during the exposure period. Paraquat is a highly toxic herbicide that inflicts at least part of its damage by generating free radicals.

http://www.ncbi.nlm.nih.gov/pubmed/7776173

Cancer Family Physician • May 1993

Mutagens and carcinogens in foods
Epidemiologic review

By T.G. Hislop

Abstract

“Evidence that diet contributes to the development of cancer is strengthening. This paper examines mutagens and carcinogens, such as naturally occurring substances, products of cooking and food processing, intentional and unintentional additives, and contaminants, found in foods. Such substances are present in minute quantities in the diets of average Canadians. Indication of health risk is largely limited to experimental laboratory evidence.”

Full text, graphs, charts and 31 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2379645/

Critical Reviews In Biochemistry And Molecular Biology • November 1992

Aldehyde dehydrogenases and their role in carcinogenesis

Author information

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Abstract

Aldehydes are highly reactive molecules that may have a variety of effects on biological systems. They can be generated from a virtually limitless number of endogenous and exogenous sources. Although some aldehyde-mediated effects such as vision are beneficial, many effects are deleterious, including cytotoxicity, mutagenicity, and carcinogenicity. A variety of enzymes have evolved to metabolize aldehydes to less reactive forms. Among the most effective pathways for aldehyde metabolism is their oxidation to carboxylic acids by aldehyde dehydrogenases (ALDHs). ALDHs are a family of NADP-dependent enzymes with common structural and functional features that catalyze the oxidation of a broad spectrum of aliphatic and aromatic aldehydes. Based on primary sequence analysis, three major classes of mammalian ALDHs--1, 2, and 3--have been identified. Classes 1 and 3 contain both constitutively expressed and inducible cytosolic forms. Class 2 consists of constitutive mitochondrial enzymes. Each class appears to oxidize a variety of substrates that may be derived either from endogenous sources such as amino acid, biogenic amine, or lipid metabolism or from exogenous sources, including aldehydes derived from xenobiotic metabolism. Changes in ALDH activity have been observed during experimental liver and urinary bladder carcinogenesis and in a number of human tumors, including some liver, colon, and mammary cancers. Changes in ALDH define at least one population of preneoplastic cells having a high probability of progressing to overt neoplasms. The most common change is the appearance of class 3 ALDH dehydrogenase activity in tumors arising in tissues that normally do not express this form. The changes in enzyme activity occur early in tumorigenesis and are the result of permanent changes in ALDH gene expression. This review discusses several aspects of ALDH expression during carcinogenesis. A brief introduction examines the variety of sources of aldehydes. This is followed by a discussion of the mammalian ALDHs. Because the ALDHs are a relatively understudied family of enzymes, this section presents what is currently known about the general structural and functional properties of the enzymes and the interrelationships of the various forms. The remainder of the review discusses various aspects of the ALDHs in relation to tumorigenesis. The expression of ALDH during experimental carcinogenesis and what is known about the molecular mechanisms underlying those changes are discussed. This is followed by an extended discussion of the potential roles for ALDH in tumorigenesis. The role of ALDH in the metabolism of cyclophosphamidelike chemotherapeutic agents is described. This work suggests that modulation of ALDH activity may be an important determinant of the effectiveness of certain chemotherapeutic agents.

http://www.ncbi.nlm.nih.gov/pubmed/1521460

“Food additives, drugs, and other chemicals are known to influence the lower gastrointestinal tract under some defined conditions, resulting in morphological alterations in the mucosa and other tissues, deranged absorption and excretion of nutrients, and, in some cases, injury to other organs and tissues as a secondary phenomenon.”

Toxicology And Pathology • December 1988

The influence of food additives and related materials on lower bowel structure and function

Author information

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Abstract

Food additives, drugs, and other chemicals are known to influence the lower gastrointestinal tract under some defined conditions, resulting in morphological alterations in the mucosa and other tissues, deranged absorption and excretion of nutrients, and, in some cases, injury to other organs and tissues as a secondary phenomenon. Generally, in rats, hamsters, and dogs, there is increased absorption and urinary excretion of calcium, soft stools or diarrhea, and cecal enlargement. In the rat, hamster, and dog, renal lesions accompany the hypercalcemia and elevated excretion of calcium. These signs, symptoms, and lesions are typical of exposure to sugar alcohols (sorbitol, mannitol, xylitol, lactitol), lactose and caramel, some of the chemically modified food starches, and synthetic polydextrose. Soft stools and diarrhea, as well as cecal enlargement and variable hyperplasia of the colon mucosa, occur frequently when substances are absorbed incompletely in the small intestine and subjected to microbial metabolism in the cecum and colon. The remarkable cecal enlargement, mucosal hyperplasia and, when present, colonic mucosal hyperplasia are reversible, even when long-standing. Renal lesions are reversible only if exposure is of short duration, before significant mineralization and scarring has occurred. Morphological and functional anomalies associated with some of these substances are described and illustrated.

Full text, downloadable PDF, graphs, charts, great photos with 29 references

http://tpx.sagepub.com/content/16/2/184.long

Surgical Clinics Of North America • October 1986

The role of non-nutritive dietary constituents in carcinogenesis

Palmer S, Mathews RA.

Abstract

“Very low levels of a large variety of non-nutritive chemicals occur in the diet. Among those that occur naturally are metabolites of molds (for example, mycotoxins) and bacteria (for example, nitrosamines) and natural constituents of plants (for example, pyrrolizidine alkaloids). Many of these are occasional contaminants, whereas others are normal components of relatively common foods. Some compounds (for example, aflatoxin, nitrosamines, and hydrazones) have been found to be carcinogenic in laboratory animals and mutagenic in bacterial and other systems, thereby posing a potential risk to humans. However, there have been very few definitive epidemiologic studies. Therefore, further investigations are necessary to determine the significance of these experimental findings for humans. It is apparent that many foods naturally contain substances with mutagenic properties and that some substances found in foods can enhance or inhibit the mutagenic activity of other compounds. Furthermore, mutagens can be formed during the cooking or processing of foods. However, caution is needed in the interpretation of these findings. Although mutagens by definition are “suspect” carcinogens, many mutagens detected in foods have not been adequately tested for carcinogenicity, and therefore their significance for human health cannot be fully assessed. With the exception of studies on non-nutritive sweeteners like saccharin and cyclamate, or those on nitrate and nitrite, very few epidemiologic studies have been conducted to examine the effect of food additives on cancer risk. Of the few direct food additives that have been tested and found to be carcinogenic in animals, all except saccharin have been banned from use in the food supply. Minute residues of a few indirect additives that are known either to produce cancer in animals (for example, vinyl chloride and acrylonitrile) or to be carcinogenic in humans (for example, vinyl chloride) are occasionally detected in foods. Thus far, the increasing use of food additives does not seem to have contributed significantly to the overall cancer risk for humans. However, the relatively short duration of use of many of these substances and the inadequacy of the data base preclude definitive conclusions. Very low levels of a large and chemically diverse group of substances—environmental contaminants (for example, residues of pesticides, polycyclic aromatic hydrocarbons, and traces of toxic metals)—may be present in foods.”

http://www.ncbi.nlm.nih.gov/pubmed/3532377

Cancer • October 1986

Carcinogens and mutagens that may occur in foods

Miller EC, Miller JA.

Abstract

"The principal carcinogens and mutagens that have been identified in human foods are reviewed. These agents may occur in foods as naturally occurring components (e.g., metabolites made by plant or fungal cells), components of contaminating plants or microorganisms, food additives (usually unintentional), or products that arise during processing or cooking. In the mixed diets of developed countries the levels of the known carcinogens and mutagens are very low. However, serious contamination of foods by the potent hepatocarcinogen aflatoxin B1 has occurred in some parts of the world; contamination by N-nitroso compounds or their precursors is another important concern. Extrapolation of the data on the carcinogenicity and mutagenicity of chemicals that can occur in foods to an accurate estimation of the potential hazard to human populations is not yet possible."

http://www.ncbi.nlm.nih.gov/pubmed/3756803

“These results indicate that sodium sorbate is a genotoxic agent, although its potency seems to be weak, and that sorbic acid and potassium sorbate are less genotoxic than the sodium salt.”

Food Chemistry And Toxicology • July 1984

Effects of sorbic acid and its salts on chromosome aberrations, sister chromatid exchanges and gene mutations in cultured Chinese hamster cells

Hasegawa MM, Nishi Y, Ohkawa Y, Inui N.

Abstract

The ability of sorbic acid and its potassium and sodium salts to induce chromosome aberrations, sister chromatid exchanges (SCE) and gene mutations in cultured Chinese hamster V79 cells was examined. Sodium sorbate caused significant induction of chromosome aberrations and SCE, and also induced 6-thioguanine-resistant mutations in a dose-dependent manner. The clastogenic potency of sodium sorbate was found to be less than one hundredth of that of the potent clastogen N-methyl-N’-nitro-N-nitrosoguanidine. The induction of SCE by sodium sorbate was twice the control level, whereas that by methyl methanesulphonate, a potent inducer of SCE, was 14 times the control level. The mutagenic potency of sodium sorbate was less than one-tenth that of ethyl methanesulphonate, a potent inducer of mutation, when compared at an equitoxic level. Sorbic acid and its potassium salt induced chromosome aberrations, but only at the highest doses tested. These compounds also induced 1.2 times the control level of SCE, but neither compound induced 6-thioguanine-resistant mutations. The cytogenetic activity of sodium sorbate was concluded not to be due to the effect of osmotic pressure or an impurity. These results indicate that sodium sorbate is a genotoxic agent, although its potency seems to be weak, and that sorbic acid and potassium sorbate are less genotoxic than the sodium salt.

http://www.ncbi.nlm.nih.gov/pubmed/6540226

Cancer Letters • October 1984

Studies on the promoting and complete carcinogenic activities of some oxidizing chemicals in skin carcinogenesis

Kurokawa Y, Takamura N, Matsushima Y, Imazawa T, Hayashi Y.

Abstract

“Six oxidizing chemicals were tested for promoting and complete carcinogenic activities in skin carcinogenesis using female Sencar mice. In the promotion tests, the chemicals were applied twice a week for 51 weeks after initiation with dimethylbenzanthracene (DMBA). In the tests for complete carcinogenic activities, the chemicals alone were applied for 51 weeks. Benzoyl peroxide was found to be a potent promoter as reported previously. Moreover, possible complete carcinogenic action of this chemical was found in this study. Potential promoting effect was suspected in sodium chlorite. Potassium bromate, ammonium persulphate, hydrogen peroxide and sodium hypochlorite were inactive either as a promoter or a complete carcinogen.”

http://www.ncbi.nlm.nih.gov/pubmed/6437666

Critical Reviews In Food Science And Nutrition • 1980

Nonenzyme browning and its effect on protein nutrition

Dworschák E.

Abstract

The nonenzyme browning involves the thermal decomposition of sugars, the caramelization, the decomposition of oxi-acids, the so called "Maillard reaction" between amino acids and carbohydrates, the reaction between oxidized fats and proteins, and those alterations which take place by the alkaline treatment of proteins. The Maillard reaction is of secondary importance in the case of foodstuffs and fodders with low carbohydrate contents (meats, meat meal, fish meal). By the heat treatment, the sulphur-containing amino acids of proteins (cystine, methionine) are damaged primarily because of oxidation, but the decrease in the amount of threonine, serine, tryptophan, and lysine is observable too. According to the formation of enzyme resistant cross-links, the in vitro and in vivo digestibility of protein decreases after the heat threatment and the communication with oxidized fats. Besides the amino acids mentioned, the possibility of enzymatic break-off of leucine and isoleucine is reduced too. In the course of the heating of proteins the occurance of racemization has to be considered too (formation of alloisoleucine). The basic mechanism of the reaction between sugars and simple amino acids is already essentially explained: amino-acids break off after the formation glycosilamines and Amadori products but they are linked irreversibly to some, partly unsaturated decomposition products of sugars, types of 6 and 3 carbon atoms. The decrease in the biological usability of amino acids starts already with the Amadori products. The reactivity of the single amino acids depends on the number of carbon atoms, on the basicity, and on the polarity of the amino acid molecule. The especially highly reactive amino acids of proteins are (1) the essential lysine (because of its 6-HN2 group), (2) other types of basic amino acids, and (3) trypotphan (because of the lability of the indole ring), methionine, cystine and threonine. In the Maillard reaction of tryptophan the --NH--group of the indole ring is involved too. The Maillard reaction is highly influenced by the pH of foodstuffs or other agents. The reduction of pH which may be performed by the increase of fermentation in the baking industry, lessens the decomposition of lysine and tryptophan in proteins. The raise of pH in basic domain enhances the Maillard reaction up to a maximal value but a decrease may be observed when the pH is raised further on. In foodstuffs and in other solid protein-carbohydrate systems the increase of the moisture content generally enhances the Maillard reaction, the sensibility of the single amino acids to the changes int he moisture content is different. In the case of the alkaline treatment of proteins, we must reckon not only with the decomposition of single amino acids, first of all that of cystine by beta-elimination, but with the formation of some amino acid derivatives as lysinoalanine, lanthionine, and in ornithinoalanine too. Presently lysinoalanine is of toxicological importance as proved by experiences on rats...

http://www.ncbi.nlm.nih.gov/pubmed/6996923

Cancer • May 1979

Food additives (natural and synthetic)

By P. Shubik

Abstract

“Food additives can be divided into the following categories: intentional, unintentional, contaminants, and those resulting from food processing procedures. Representative food additives from each category are discussed, with special attention being paid to the status of those suspected or proven to be toxic to humans. In addition, certain chemical components of food and methods for testing food additives are considered. Areas requiring additional testing include saccharin, cooking procedures, especially charcoal broiling, and hydrozines in mushrooms. The more recent developments in test procedures, including in vitro test methods, the transplacental exposure route, the use of maximal tolerated dose, and the initiation--promotion sequence, are evaluated.”

Full text PDF with 23 references

http://onlinelibrary.wiley.com/store/10.1002/1097-0142(197905)43:5%2B%3C1982::AID-CNCR2820430705%3E3.0.CO;2-H/asset/2820430705_ftp.pdf?v=1&t=iph3ygir&s=4b922f2f7541a6bbe829cec9cc3ddc3909e92b9a

“Sulphur dioxide has not previously been reported to cause exacerbations of asthma when ingested as a food preservative. It is used as a preservative in a wide range of acidic beverages and foods, and should be considered as possibly causal in patients suffering from apparently cryptogenic asthma, and asthma seemingly due to food allergy.”

Clinical Allergy • September 1977

Asthma induced by sulphur dioxide, benzoate and tartrazine contained in orange drinks

By B.J. Freedman

Abstract

Of 272 patients with asthma, thirty (11%) gave a history of exacerbations occurring after ingestion, solutions of orange orange drinks. Fourteen of these were given provocation tests by drinking, on separate occasions of sulphur dioxide, sodium benzoate and tartrazine, which are present in all orange drinks. Eight reacted to sulphur dioxide with a fall in FEV1, four to sodium benzoate and one to tartrazine, and four did not react to any of these agents. Three of the benzoate patients were also sensitive to sulphur dioxide. The sulphur dioxide sensitive patients were predominantly young, with extrinsic asthma. The benzoate sensitive patients were predominantly middle-aged and the proportion with intrinsic asthma was higher. Prior inhalation of sodium cromoglycate by four patients inhibited the reaction to these substances. Sulphur dioxide has not previously been reported to cause exacerbations of asthma when ingested as a food preservative. It is used as a preservative in a wide range of acidic beverages and foods, and should be considered as possibly causal in patients suffering from apparently cryptogenic asthma, and asthma seemingly due to food allergy.

http://www.ncbi.nlm.nih.gov/pubmed/412611

CHAPTER THIRTY-EIGHT

Topicals • Sunscreen, UV Filters & Insect Repellent

The Peer Review

Fully 80 percent of 1,700 products examined this year by the Environmental Working Group offer inferior sun protection or contain worrisome ingredients like oxybenzone and vitamin A

EWG Sunscreen Hall of Shame

There are a lot of sunscreens on the market: some good, some bad and then the shameful. Those in the last category are not only a waste of money and time but also potentially harmful. Here are our picks for products to banish from your beach bag. Convenient? Yes. Good for kids? Absolutely not.

- Spray sunscreens can be inhaled, and they don't cover skin completely.
- SPF values above 50+ try to trick you into believing they'll prevent sun damage. Don't trust them. SPF protection tops out at 30 to 50.
- Oxybenzone can disrupt the hormone system.
- Retinyl palmitate may trigger damage, possibly cancer.

11 Worst Spray Sunscreens

These sunscreens are aerosol sprays with SPFs above 50+ and additives oxybenzone and retinyl palmitate

Banana Boat Clear UltraMist MAX Skin Protect Continuous Spray Sunscreen, SPF 110
Coppertone Sport High Performance AccuSpray Sunscreen, SPF 70
Coppertone Sport High Performance Clear Continuous Spray Sunscreen, SPF 100+
CVS Clear Spray Sunscreen, SPF 100
CVS Sheer Mist Spray Sunscreen, SPF 70
CVS Sport Clear Spray Sunscreen, SPF 100+
CVS Wet & Dry Sunscreen Spray, SPF 85
Neutrogena Fresh Cooling Sunscreen Body Mist, SPF 70
Neutrogena Ultra Sheer Body Mist Sunscreen Spray, SPF 100+
Neutrogena Ultra Sheer Body Mist Sunscreen Spray, SPF 70
Neutrogena Wet Skin Sunscreen Spray, SPF 85+

12 Worst Sunscreen Lotions

These sunscreen lotions claim SPFs above 50+ and contain oxybenzone and retinyl palmitate

Banana Boat Sport Performance Sunscreen Lotion, SPF 100
Coppertone Sport High Performance Sunscreen Lotion, SPF 100
Coppertone Sport High Performance Sunscreen, SPF 75
Coppertone Sport Sunscreen Stick, SPF 55
Coppertone Ultra Guard Sunscreen Lotion, SPF 70+
CVS Sport Sunstick Sunscreen, SPF 55
CVS Sun Lotion Sunscreen, SPF 100
CVS Sun Lotion Sunscreen, SPF 70
Neutrogena Ultra Sheer Daily Liquid Sunscreen, SPF 70
NO-AD Sunscreen Lotion, SPF 60
NO-AD Sunscreen Lotion, SPF 85
Ocean Potion Protect & Nourish Sunscreen Lotion, SPF 70

11 Worst Sunscreens for Kids

These terrible infant sunscreens have three strikes against them: 1 oxybenzone, 2 retinyl palmitate and 3 SPFs above 50+. Two have a 4th strike: they're aerosol sprays that can harm sensitive young lungs.

BananaBoat Clear UltraMist KidsMax Protect & Play Cont. Spray Sunscreen, SPF 110
Coppertone Kids Sunscreen Lotion, SPF 70
Coppertone Kids Sunscreen Stick, SPF 55
Coppertone Kids Wacky Foam Foaming Lotion Sunscreen, SPF 70+
Coppertone Water Babies Sunscreen Lotion, SPF 70+
Coppertone Water Babies Sunscreen Stick, SPF 55
Equate Kids Sunscreen Stick, SPF 55
Kroger Baby Sunscreen Lotion, SPF 70
Kroger Kids Sunscreen Lotion, SPF 70
Neutrogena Wet Skin Kids Beach & Pool Sunblock Spray, SPF 70+
Up & Up Kid's Sunscreen Stick, SPF 55

How EWG picked the Hall of Shame

1) Spray sunscreens

One in every four sunscreens in this year's database is a spray. People like sprays because they're easy to squirt on squirming kids and hard-to-reach areas. But they may pose serious inhalation risks, and they make it too easy to apply too little or miss a spot. The FDA has expressed doubts about their safety and effectiveness but hasn't banned them. As long as they're legal and we continue to buy them, chemical manufacturers will continue to make them.

2) Sky-high SPFs

One eighth of the sunscreens we evaluated this year boast SPFs above 50+. SPF stands for "sun protection factor," but that outdated term refers only to protection against UVB rays that burn the skin. It has little to do with a product's ability to protect skin from UVA rays, which penetrate deep into the body, accelerate skin aging, may suppress the immune system and may cause skin cancer. The worst thing about high-SPF products is that they give people a false sense of security and tempt them to stay in the sun too long. They suppress sunburns but raise the risk of other kinds of skin damage. The FDA is considering barring SPF above 50+.

3) Oxybenzone

Half of the beach and sport sunscreens in this year's guide contain oxybenzone, an active ingredient in sunscreens. But it penetrates the skin, gets into the bloodstream and acts like estrogen in the body. It can trigger allergic skin reactions. Some research studies, while not conclusive, have linked higher concentrations of oxybenzone to disorders, including endometriosis in older women and, lower birth weights in newborn girls.

4) Retinyl palmitate

Nearly 20 percent of the sunscreens and SPF-rated moisturizers and 13 percent of SPF-rated lip products in this year's guide contain retinyl palmitate, a form of vitamin A. Night creams with this chemical may help skin look more youthful. But on sun-exposed skin, retinyl palmitate may speed development of skin tumors and lesions, according to government studies. Why does the FDA allow this "inactive ingredient" in sunscreens intended for use in the sun? The agency has been studying the chemical for years but hasn't made a decision. We have. The definitive study may not have been done, but we think we know enough to believe you're better off without sunscreens with retinyl palmitate.

“Nanoscale ingredients in commercial products represent a point of emerging environmental concern due to recent findings that correlate toxicity with small particle size.”

Journal Of Exposure Science And Environmental Epidemiology • January 2016

A weight-of-evidence approach to identify nanomaterials in consumer products: a case study of nanoparticles in commercial sunscreens

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Abstract

Nanoscale ingredients in commercial products represent a point of emerging environmental concern due to recent findings that correlate toxicity with small particle size. A weight-of-evidence (WOE) approach based upon multiple lines of evidence (LOE) is developed here to assess nanomaterials as they exist in consumer product formulations, providing a qualitative assessment regarding the presence of nanomaterials, along with a baseline estimate of nanoparticle concentration if nanomaterials do exist. Electron microscopy, analytical separations, and X-ray detection methods were used to identify and characterize nanomaterials in sunscreen formulations. The WOE/LOE approach as applied to four commercial sunscreen products indicated that all four contained at least 10% dispersed primary particles having at least one dimension <100 nm in size. Analytical analyses confirmed that these constituents were comprised of zinc oxide (ZnO) or titanium dioxide (TiO2). The screening approaches developed herein offer a streamlined, facile means to identify potentially hazardous nanomaterial constituents with minimal abrasive processing of the raw material.

http://www.ncbi.nlm.nih.gov/pubmed/26374657

Science Reports • June 2016

The insect repellent N,N-diethyl-m-toluamide (DEET) induces angiogenesis via allosteric modulation of the M3 muscarinic receptor in endothelial cells

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Abstract

"The insect repellent N,N-diethyl-m-toluamide (DEET) has been reported to inhibit AChE (acetylcholinesterase) and to possess potential carcinogenic properties with excessive vascularization. **In the present paper, we demonstrate that DEET specifically stimulates endothelial cells that promote angiogenesis which increases tumor growth. DEET activates cellular processes that lead to angiogenesis including proliferation, migration and adhesion.** This is associated with an enhancement of NO production and VEGF expression in endothelial cells. M3 silencing or the use of a pharmacological M3 inhibitor abrogates all of these effects which reveals that DEET-induced angiogenesis is M3 sensitive. The experiments involving calcium signals in both endothelial and HEK cells overexpressing M3 receptors, as well as binding and docking studies demonstrate that DEET acts as an allosteric modulator of the M3 receptor. In addition, DEET inhibited AChE which increased acetylcholine bioavailability and binding to M3 receptors and also strengthened proangiogenic effects by an allosteric modulation."

Full text, graphs, charts and 59 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4921870/

“Sunscreen products and some personal care products contain the Ultraviolet (UV) chemical filters, which are entering the surface water. Public concerns about secondary effects of these compounds are growing because of the contamination of the aquatic environment that may reach to potentially toxic concentration levels. **Therefore, this article calls for an urgent investigation of potential toxic effects of the UV filters, the creation of disinfection by products and their subsequent impacts on human health.**”

Environmental Research • July 2016

UV filters interaction in the chlorinated swimming pool, a new challenge for urbanization, a need for community scale investigations

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Abstract

Sunscreen products and some personal care products contain the Ultraviolet (UV) chemical filters, which are entering the surface water. Public concerns about secondary effects of these compounds are growing because of the contamination of the aquatic environment that may reach to potentially toxic concentration levels. This article highlights the reaction of certain UV filters with hypochlorite disinfectant in the presence of sunlight. Due to urbanization and industrialization, use of outdoor plastic swimming pools is increasing. The relatively smaller volume of these pools compared to larger pools may increase the concentration of the UV filters in the pool and their potential interactions with materials of human origin (urine, sweat, cosmetics, skin cells, and hair) to the levels of toxicity concerns for children through the creation of disinfection by products (DBP). Based on our analysis, the minimum concentration levels of 2.85, 1.9, 1.78 and 0.95g/L, respectively, for EHMC, OC, 4-MBC and BP3 UV filters in children pools are predicted. Therefore, this article calls for an urgent investigation of potential toxic effects of the UV filters, the creation of DBPs and their subsequent impacts on human health.

http://www.ncbi.nlm.nih.gov/pubmed/27088731

Journal Of Dermatological Treatment • September 2016

Percutaneous penetration and pharmacodynamics: Wash-in and wash-off of sunscreen and insect repellent

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Abstract

"Increased awareness of skin cancer and mosquito-transmitted diseases has increased use of insect repellents and sunscreens. The challenge in setting recommendations for use and reapplication, especially when used concomitantly, lies in finding the balance between applying a durable product effective in withstanding natural and physical factors such as water, sweat, temperature and abrasion, while limiting percutaneous absorption and decreasing risk of potential dermal and systemic toxicity. Inorganic sunscreens show no or little percutaneous absorption or toxic effects in comparison to organic sunscreens, which show varying levels of dermal penetration and cutaneous adverse effects. An alternative to N,N-diethyl-m-toluamide (DEET), the traditional gold standard compound in insect repellents, picaridin appears as efficacious, has lower risk of toxicity, and when used simultaneously with sunscreen may decrease percutaneous absorption of both compounds. Conversely, combined use of DEET and sunscreen results in significantly higher absorption of both compounds. It is important to increase consumer awareness of "washing in" of various compounds leading to increased risk of toxicity, as well as differences in reapplication need due to "washing off" caused by water, sweat and abrasion. Although much remains to be studied, to maximize efficacy and decrease toxicity, contemporary research tools, including dermatopharmokinetics, should aid these prospective advances."

http://www.ncbi.nlm.nih.gov/pubmed/26811157

“The assay data provide strong evidence that **titanium dioxide nanoparticles can induce cytotoxicity, significant DNA damage, and apoptosis of A549 cells, suggesting that exposure to titanium dioxide nanoparticles could cause cell injury and be hazardous to health.**”

Environmental Science And Pollution Research International • April 2015

Cytotoxicity, DNA damage, and apoptosis induced by titanium dioxide nanoparticles in human non-small cell lung cancer A549 cells

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Abstract

Concerns about the risk of titanium dioxide nanoparticles (TiO2 NPs) to human health and environment are gradually increasing due to their wide range of applications. In this study, cytotoxicity, DNA damage, and apoptosis induced by TiO2 NPs (5 nm) in A549 cells were investigated. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays revealed the time- and concentration-dependent cytotoxic effects of TiO2 NPs in a concentration range of 50 to 200 μg/mL. A statistically significant ($p<0.05$) induction in DNA damage was observed by the comet assay in cells exposed to 50 to 200 μg/mL TiO2 NPs for 48 h. A significant ($p<0.05$) induction in micronucleus formation determined by 4,6-diamino-2-phenylindole (DAPI) staining was also observed at the above concentrations. Typical apoptotic morphological feature and apoptotic bodies in A549 cells induced by TiO2 NPs at the above concentrations were observed by scanning electron micrographs. Flow cytometric analysis demonstrated that the cells treated with TiO2 NPs at concentrations of 100 and 200 μg/mL showed a significant G2/M phase arrest and a significant increased proportion of apoptotic cells. TiO2 NPs also disrupted the mitochondrial membrane potential evaluated by rhodamine 123 staining. Further analysis by quantitative real-time PCR (qRT-PCR) indicated that the expression of caspase-3 and caspase-9 messenger RNA (mRNA) was increased significantly at the concentrations of 100 and 200 μg/mL TiO2 NPs for 48 h. Taken together, these findings suggest that TiO2 NPs can inhibit A549 cell proliferation, cause DNA damage, and induce apoptosis via a mechanism primarily involving the activation of the intrinsic mitochondrial pathway. The assay data provide strong evidence that TiO2 NPs can induce cytotoxicity, significant DNA damage, and apoptosis of A549 cells, suggesting that exposure to TiO2 NPs could cause cell injury and be hazardous to health.

http://www.ncbi.nlm.nih.gov/pubmed/25339530

“Transport of ultrafine titanium dioxide nanoparticles in systemic circulation and further transition through barriers, especially the placental and blood-brain ones, are well documented.
Therefore, from the developmental point of view, there is a raising concern in the exposure to titanium dioxide nanoparticles during critical windows, in the pregnancy or the lactation period, and the fact that human mothers, women and men in fertile age and last but not least children may be exposed to high cumulative doses.”

Endocrine Regulations • April 2015

Titanium dioxide nanoparticles:
some aspects of toxicity/focus on the development

Rollerova E, Tulinska J, Liskova A, Kuricova M, Kovriznych J, Mlynarcikova A, Kiss A, Scsukova S.

Abstract

Nanosized titanium dioxide (TiO2) particles belong to the most widely manufactured nanoparticles (NPs) on a global scale because of their photocatalytic properties and the related surface effects. TiO2 NPs are in the top five NPs used in consumer products. Ultrafine TiO2 is widely used in the number of applications, including white pigment in paint, ceramics, food additive, food packaging material, sunscreens, cosmetic creams, and, component of surgical implants. Data evidencing rapid distribution, slow or ineffective elimination, and potential long-time tissue accumulation are especially important for the human risk assessment of ultrafine TiO2 and represent new challenges to more responsibly investigate potential adverse effects by the action of TiO2 NPs considering their ubiquitous exposure in various doses. Transport of ultrafine TiO2 particles in systemic circulation and further transition through barriers, especially the placental and blood-brain ones, are well documented. Therefore, from the developmental point of view, there is a raising concern in the exposure to TiO2 NPs during critical windows, in the pregnancy or the lactation period, and the fact that human mothers, women and men in fertile age and last but not least children may be exposed to high cumulative doses. In this review, toxicokinetics and particularly toxicity of TiO2 NPs in relation to the developing processes, oriented mainly on the development of the central nervous system, are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/25960011

“Caution should be taken in exposing the skin to airborne dust due to its ability to reduce barrier function and increase the risk of drug overabsorption ...”

Journal Of Dermatology Science • April 2015

The impact of urban particulate pollution on skin barrier function and the subsequent drug absorption

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Abstract

BACKGROUND
Ambient particulate matters (PMs) are known as inducers that adversely affect a variety of human organs.
OBJECTIVES
In this study, we aimed to evaluate the influence of PMs on the permeation of drugs and sunscreens via the skin. The role of skin-barrier properties such as the stratum corneum (SC) and tight junctions (TJs) during the delivery process was explored.
METHODS
This work was conducted using both in vitro and in vivo experiments in pigs to check the responses of the skin to PMs. PMs primarily containing heavy metals (1648a) and polycyclic aromatic hydrocarbons (PAHs, 1649b) were employed to treat the skin.
RESULTS
According to the transepidermal water loss (TEWL), 1649b but not 1648a significantly disrupted the SC integrity by 2-fold compared to the PBS control. The immunohistochemistry (IHC) of cytokeratin, filaggrin, and E-cadherin exhibited that 1649b mildly damaged TJs. The cytotoxicity of keratinocytes and skin fibroblasts caused by 1649b was stronger than that caused by 1648a. The 1649b elicited apoptosis via caspase-3 activation. The proteomic profiles showed that PMs upregulated Annexin A2 by >5-fold, which can be a biomarker of PM-induced barrier disruption. We found that the skin uptake of ascorbic acid, an extremely hydrophilic drug, was increased from 74 to 112 µg/g by 1649b treatment. The extremely lipophilic drug tretinoin also showed a 2.6-fold increase of skin accumulation. Oxybenzone and dextran absorption was not affected by PMs. The in vivo dye distribution visualized by fluorescence microscopy had indicated that 1649b intervention promoted permeant partitioning into SC.
CONCLUSIONS
Caution should be taken in exposing the skin to airborne dust due to its ability to reduce barrier function and increase the risk of drug overabsorption, although this effect was not very marked.

http://www.ncbi.nlm.nih.gov/pubmed/25680853

“The wide uses of zinc oxide nanoparticles (nano-ZnO) in industrial, cosmetics, medicine, food production and electronics associate with increase in occupational and public exposure. **Zinc oxide nanoparticles caused statistically significant DNA damage**. Our results highlight the important risk of cyto- and genotoxic effects of zinc oxide nanoparticles over the kidney.”

Toxicology Mechanisms And Methods • May 2015

Zinc oxide nanoparticles induced cyto- and genotoxicity in kidney epithelial cells

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Abstract

The wide uses of zinc oxide nanoparticles (nano-ZnO) in industrial, cosmetics, medicine, food production and electronics associate with increase in occupational and public exposure. Although, toxicity of nano-ZnO has been extensively studied on many different cell types and animal systems, there is a significant lack of toxicological data focus on nephrotoxic potential of nano-ZnO. In this study, the cyto- and genotoxic effects of nano-ZnO on rat kidney epithelial cells (NRK-52E) were investigated by using different assays. Nano-ZnO (10-50 nm of sizes) were synthesized by sol-gel method. For the cytotoxic effect of nano-ZnO, mean of inhibition concentration (IC50) values in cell line was evaluated by MTT, Trypan Blue (TB) and Neutral Red Uptake (NRU) assays at 25.0-100.0 µg/mL exposure concentrations. Nano-ZnO showed cytotoxic activity by acting on different targets in renal cells, with IC50 ≥ 73.05 µg/mL. Comet assay was used to evaluate the genotoxicity of nano-ZnO (12.5-50.0 µg/mL). Nano-ZnO caused statistically significant DNA damage. Our results highlight the important risk of cyto- and genotoxic effects of nano-ZnO over the kidney.

http://www.ncbi.nlm.nih.gov/pubmed/25980654

“A severe to slight damage was observed in liver tissue in all groups and tissue destruction was seen in kidney only in acute dose treated groups ...”

Bratislavske Lekarske Listy • July 2015

Toxic effect of nano-zinc oxide

Espanani HR, Faghfoori Z, Izadpanah M, Babadi VY.

Abstract

INTRODUCTION

Nowadays, a lot of studies were carried out about side effects of nanoparticles especially nano-zinc oxide, but unfortunately, most of these studies have been conducted with high doses.

MATERIAL AND METHODS

In the present study 36 male Wistar rats with approximate age of two months and weighing 300±30 g were selected. After standard phases of preparation, injections were done intraperitoneally in chronic groups with zinc oxide nanoparticles (20 and 40 mg/kg) every other day and for acute groups with 200 and 400 mg/kg in a single dose. After the determined time for every group (21 days for chronic groups and 7 days for acute groups), blood samples were provided from rat hearts and also liver, kidney and testicular tissue were removed for histological studies.

RESULTS

There were significant decreases in lymphocytes and platelet counts and significant increases in white blood cells count, hemoglobin and hematocrit in acute dose compared to control group and no difference in red blood cells count in all groups. A severe to slight damage was observed in liver tissue in all groups and tissue destruction was seen in kidney only in acute dose treated groups but no specific pathological effect in testis was observed.

http://www.ncbi.nlm.nih.gov/pubmed/26531873

“Studies showed that Titanium dioxide nanoparticles exposure resulted in microglia activation, reactive oxygen species production, activation of signaling pathways involved in inflammation and cell death, both in vitro and in vivo. Consequently, such action led to neuroinflammation, further brain injury. A spatial recognition memory and locomotor activity impairment has been also observed.”

Toxicology In Vitro • August 2015

Toxicity of titanium dioxide nanoparticles in central nervous system

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Abstract

Titanium dioxide nanoparticles (TiO2 NPs) have found many practical applications in industry and daily life. A widespread application of TiO2 NPs rises the question about safety of their use in the context of potential occupational, environmental and intentional exposure of humans and biota. TiO2 NPs easily enter the body through inhalation, cross blood-brain barrier and accumulate in the brain, especially in the cortex and hippocampus. Toxicity of these NPs and the molecular mechanisms of their action have been studied extensively in recent years. Studies showed that TiO2 NPs exposure resulted in microglia activation, reactive oxygen species production, activation of signaling pathways involved in inflammation and cell death, both in vitro and in vivo. Consequently, such action led to neuroinflammation, further brain injury. A spatial recognition memory and locomotor activity impairment has been also observed.

http://www.ncbi.nlm.nih.gov/pubmed/25900359

“Formulations containing 50% by weight purple carrot showed good UV blocking capabilities and represent a promising ingredient for sunscreen and cosmetic applications.”

International Journal Of Cosmetic Science • November 2015

UV blocking potential of oils and juices

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Abstract

OBJECTIVE

Sunscreens are a commonly used to protect the body from damage caused by UV light. Some components of organic sunscreens have been shown to pass through the skin during wear which could raise toxicity concerns for these compounds. This study explores the potential for oils and fruit and vegetable juices to be substitutes for these compounds.

METHODS

The absorptivity of various oils (canola oil, citronella oil, coconut oil, olive oil, soybean oil, vitamin E, as well as aloe vera) and fruit and vegetable juices (acerola, beet, grape, orange carrot, purple carrot, and raspberry) was measured in vitro. The mean absorptivity was compared with FDA approved UV absorbers to gauge the potential of the natural products. The most promising candidates were incorporated into formulations and the UV transmittance of a 20µm thick film of the formulation was measured. The formulations were also imaged by light microscopy and scanning electron microscopy.

RESULTS

The absorptivity of oils was at least two orders of magnitude lower compared to the commercial UV blockers. The fruit juice powders were more effective at UV blocking but still showed an order of magnitude lower absorptivity compared to commercial UV blockers.

CONCLUSION

The UV blocking from most natural oils is insufficient to get significant UV protection. Formulations containing 50wt% purple carrot showed good UV blocking capabilities and represent a promising ingredient for sunscreen and cosmetic applications.

http://www.ncbi.nlm.nih.gov/pubmed/26610885

“The micronucleus test revealed damage to chromosomes in rat bone marrow at 100 and 200mg/kg bw; the comet assay showed significant DNA damage at the same doses.”

Mutation Research, Genetics, Toxicology And Environmental Mutagenics • December 2015

Anemia and genotoxicity induced by sub-chronic intragastric treatment of rats with titanium dioxide nanoparticles.

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Abstract

Titanium dioxide nanoparticles (TiO2 NPs) are widely used for their whiteness and opacity. We investigated the hematological effects and genotoxicity of anatase TiO2 NPs following sub-chronic oral gavage treatment. TiO2-NPs were characterized by X-ray diffractometry (XRD), X-ray photoelectron spectroscopy (XPS), and transmission electron microscopy (TEM). Wistar rats were treated with anatase TiO2 NPs by intragastric administration for 60 days. Hematological analysis showed a significant decrease in RBC and HCT and a significant increase in MCV, PLT, MPV and WBC at higher doses. Furthermore, abnormally shaped red cells, sometimes containing micronuclei, and hyper-segmented neutrophil nuclei were observed with TiO2 NPs treatment. The micronucleus test revealed damage to chromosomes in rat bone marrow at 100 and 200mg/kg bw; the comet assay showed significant DNA damage at the same doses.

http://www.ncbi.nlm.nih.gov/pubmed/26653980

“These findings suggest sunscreen user to avoid Benzophenone-1 in cosmetics preparation for its topical application.”

Toxicology Letters • December 2015

Benzophenone 1 induced photogenotoxicity and apoptosis via release of cytochrome c and Smac/DIABLO at environmental UV radiation

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Abstract

Solar UV radiation is main factor of photocarcinogenesis, photoageing, and phototoxicity; thus, protection from UV radiation is major concern. Sunscreens containing UV filters are suggested as sun safe practices, but safety of UV filters remains in controversies. Benzophenone-1 (BP1) is commonly used in sunscreens as UV blocker. We assessed the photogenotoxicity and apoptotic parameters in human keratinocytes (HaCaT cells) by western blot, immunocytochemistry, flowcytometry, comet assay and TEM imaging. Our results exposed that BP1 photosensitized and generated intracellular ROS (2.02 folds) under sunlight/UVR. Decrease in cell viability was recorded as 80.06%, 60.98% and 56.24% under sunlight, UVA and UVB, respectively. Genotoxic potential of BP1 was confirmed through photomicronuclei and CPDs formation. BP1 enhanced lipid peroxidation and leakage of LDH enzyme (61.7%). Apoptotic cells were detected by AnnexinV/PI staining and sub G1 population of cell cycle. BP1 induced up regulation of apoptotic proteins Bax/Bcl2 ratio, Apaf-1, cytochrome c, Smac/DIABLO and cleaved caspase 3 was noticed. Down regulation of pro caspase 3 was inhibited by Z-VAD-fmk (inhibitor of caspase). Thus, study established the involvement of BP1 in photogenotoxicity and apoptosis via release of cytochrome c and Smac/DIABLO. These findings suggest sunscreen user to avoid BP1 in cosmetics preparation for its topical application.

http://www.ncbi.nlm.nih.gov/pubmed/26440554

“These results may provide basic experimental evidence for a better understanding of the neurotoxic effects of Titanium dioxide nanoparticles on neonatal and adult brains.”

Environmental Toxicology And Pharmacology • March 2014

Maternal exposure to titanium dioxide nanoparticles during pregnancy; impaired memory and decreased hippocampal cell proliferation in rat offspring

Author information

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Abstract

Titanium dioxide nanoparticles (TiO2-NPs) are massively produced in the environment, and because of their wide usage, they are a potential risk of damage to human health. TiO2-NPs are often used as additives for paints, papers, and foods. The central nervous system (CNS), including hippocampal regions, is potentially susceptible targets for TiO2-NPs. This study aimed to determine the effects of exposure to TiO2-NPs during pregnancy on hippocampal cell proliferation and the learning and memory of offspring. Pregnant Wistar rats received intragastric TiO2-NPs (100 mg/kg body weight) daily from gestational day (GD) 2 to (GD) 21. Animals in the control group received the same volume of distilled water via gavage. After delivery, the one-day-old neonates were deeply anesthetized and weighed. They were then killed and the brains of each group were collected. Sections of the brains from the rat offspring were stained using Ki-67 immunolabeling and the immunohistochemistry technique. Some of the male offspring (n=12 for each group) were weaned at postnatal day (PND21), and housed until adulthood (PND60). Then the learning and memory in animals of each group were evaluated using passive avoidance and Morris water maze tests. The immunolabeling of Ki-67 protein as a proliferating cell marker showed that TiO2-NPs significantly reduced cell proliferation in the hippocampus of the offspring ($P<0.05$). Moreover, both the Morris water maze test and the passive avoidance test showed that exposure to TiO2-NPs significantly impaired learning and memory in offspring ($P<0.05$). These results may provide basic experimental evidence for a better understanding of the neurotoxic effects of TiO2-NPs on neonatal and adult brains.

http://www.ncbi.nlm.nih.gov/pubmed/24577229

“This study demonstrates a significant advance in the areas of both nanotechnology and cosmetics, developing safer cosmetic formulations that possess broad antioxidant, photoprotective and co-release effectiveness due to the existence of a high content of nanostructured vegetable oils combined with a low amount of synthetic UV filters in the same carrier system.”

Photochemical And Photobiology Science • April 2014

Rice bran and raspberry seed oil-based nanocarriers with self-antioxidative properties as safe photoprotective formulations

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Abstract

The aim of this research was to develop advanced lipid nanocarriers based on renewable vegetable resources (rice bran oil and raspberry seed oil) that possess self-antioxidative properties, having advantages in terms of minimal side effects and exhibiting the ability to simultaneously co-encapsulate and co-release two active compounds. The focus has been oriented towards developing safe cosmetic formulations with broad-spectrum photoprotection based on these new lipid nanocarriers that contain large amounts of vegetable oils and low concentrations of synthetic UVA and UVB filters (butyl-methoxydibenzoylmethane - BMDBM and octocrylene - OCT). The lipid nanocarriers have a spherical shape and show good physical stability, with a zeta potential in the range of -25.5 to -32.4 mV. Both vegetable oils play a key role in the preparation of efficient nanocarriers, leading to a less ordered arrangement of the lipid core that offers many spaces for the entrapment of large amounts of BMDBM (79%) and OCT (90%), as wells as improved antioxidant activity and UV absorption properties, particularly for the lipid nanocarriers prepared from rice bran oil. By formulating the lipid nanocarriers into creams containing only 3.5% of the UV filters and 10.5% of the vegetable oils, the resulting sunscreens exhibited improved photoprotection, reflecting up to 91% and 93% of UVA and UVB rays, respectively. A new direction of research achieved by this study is the multiple release strategy of both UV filters from the same lipid nanocarrier. After 24 hours, a slow release of BMDBM (less than 4%) and OCT (17.5%) was obtained through a Fick diffusion process. This study demonstrates a significant advance in the areas of both nanotechnology and cosmetics, developing safer cosmetic formulations that possess broad antioxidant, photoprotective and co-release effectiveness due to the existence of a high content of nanostructured vegetable oils combined with a low amount of synthetic UV filters in the same carrier system.

http://www.ncbi.nlm.nih.gov/pubmed/24590004

“This study presented a comprehensive genotoxic evaluation of titanium dioxide nanoparticles and titanium dioxide nanoparticles were shown to be genotoxic both in vivo and in vitro tests. The gene mutation and DNA strand breaks seem to be more sensitive genetic endpoints for the detection of titanium dioxide nanoparticles induced genotoxic effects.”

Toxicology Letters • May 2014

Genotoxic evaluation of titanium dioxide nanoparticles in vivo and in vitro

Author information

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Abstract

With the extensive application of titanium dioxide (TiO2) nanoparticles (NPs) in food industry, there is a rising debate concerning the possible risk associated with exposure to TiO2 NPs. The purpose of this study is to evaluate the genotoxicity of TiO2 NPs using in vivo and in vitro test systems. In vivo study, the adult male Sprague-Dawley rats were exposed to anatase TiO2 NPs (75 ± 15 nm) through intragastric administration at 0, 10, 50 and 200mg/kg body weight every day for 30 days. The ß-H2AX assay showed TiO2 NPs could induce DNA double strand breaks in bone marrow cells after oral administration. However, the micronucleus test revealed that the oral-exposed TiO2 NPs did not cause damage to chromosomes or mitotic apparatus observably in rat bone marrow cells. In vitro study, Chinese hamster lung fibroblasts (V79 cells) were exposed to TiO2 NPs at the dose of 0, 5, 10, 20, 50 and 100 µg/mL. Significant decreases in cell viability were detected in all the treated groups after 24h and 48h exposure. Significant DNA damage was only observed at the concentration of 100 µg/mL after 24h treatment using the comet assay. The obvious gene mutation was observed at the concentration of 20 and 100 µg/mL after 2h treatment using hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene mutation assay. This study presented a comprehensive genotoxic evaluation of TiO2 NPs, and TiO2 NPs were shown to be genotoxic both in vivo and in vitro tests. The gene mutation and DNA strand breaks seem to be more sensitive genetic endpoints for the detection of TiO2 NPs induced genotoxic effects.

http://www.ncbi.nlm.nih.gov/pubmed/24594277

“Our observation clearly indicates that endocrine balance and reproduction performance in fish could be affected by μg/L level exposure to Benzophenone-3.”

Aquatic Toxicology • October 2014

Effects of benzophenone-3 exposure on endocrine disruption and reproduction of Japanese medaka (Oryzias latipes)—a two generation exposure study

Author information

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Abstract

Benzophenone-3 (BP-3) has been widely used in sunscreens and cosmetics to protect human skin from the harmful effects of UV irradiation. While BP-3 has been frequently detected in surface waters, sediments and biota, only limited information is available on its in vivo toxicity, particularly in fish. In the present study the endocrine disrupting capacity of BP-3 and its underlying mechanisms were investigated using Japanese medaka (Oryzias latipes). Adult Japanese medaka pairs (F0) were exposed to 0, 4.7, 8.4, 26, or 90 μg/L (or 0, 15, 50, 150, or 500 μg/L of BP-3 based on nominal concentration) for 14 d and its effects on sex steroid hormones, and transcription of various associated genes were determined. Following additional 14 d of exposure, the F1 eggs reproduced were counted and were further exposed to 0, 5.4, 12, or 30 μg/L of BP-3 (or 0, 15, 50, or 150 μg/L based on nominal concentrations) until 30 d after hatching. Chemical analysis of the exposed media confirmed transformation of BP-3 to benzophenone-1 (BP-1), a more potent estrogen agonist. After 14 d of the adult fish exposure, plasma concentrations of testosterone (T) significantly increased in male fish. The 17□-estradiol (E2) to T (E2/T) ratio showed significant decreases in both male and female fish. Overall down-regulation of gonadal steroidogenic genes such as star, cyp11a, cyp17, hsd3b, hsd17b3, and cyp19a was also observed. After 28 d of exposure, the daily average egg reproduction per female was significantly reduced at 26 μg/L of BP-3. However, hatchability of F1 eggs was not affected by continuous exposure. After continued exposure until 30 dph, juvenile fish showed concentration-dependent decrease of condition factor, but mortality was not affected. Our observation clearly indicates that endocrine balance and reproduction performance in fish could be affected by μg/L level exposure to BP-3. Consequences of longer term exposure over multi-generations warrant further investigation.

http://www.ncbi.nlm.nih.gov/pubmed/25064457

“These results demonstrate the suitability of this method to degrade both sunscreen agents and to eliminate estrogenic activity.”

Science And The Total Environment • June 2012

Evaluation of fungal- and photo-degradation as potential treatments for the removal of sunscreens BP3 and BP1

Author information

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Abstract

Photodecomposition might be regarded as one of the most important abiotic factors affecting the fate of UV absorbing compounds in the environment and photocatalysis has been suggested as an effective method to degrade organic pollutants. However, UV filters transformation appears to be a complex process, barely addressed to date. The white rot fungus Trametes versicolor is considered as a promising alternative to conventional aerobic bacterial degradation, as it is able to metabolise a wide range of xenobiotics. This study focused on both degradation processes of two widely used UV filters, benzophenone-3 (BP3) and benzophenone-1 (BP1). Fungal treatment resulted in the degradation of more than 99% for both sunscreens in less than 24 h, whereas photodegradation was very inefficient, especially for BP3, which remained unaltered upon 24 h of simulated sunlight irradiation. Analysis of metabolic compounds generated showed BP1 as a minor by-product of BP3 degradation by T. versicolor while the main intermediate metabolites were glycoconjugate derivatives. BP1 and BP3 showed a weak, but significant estrogenic activity (EC50 values of 0.058 mg/L and 12.5 mg/L, respectively) when tested by recombinant yeast assay (RYA), being BP1 200-folds more estrogenic than BP3. Estrogenic activity was eliminated during T. versicolor degradation of both compounds, showing that none of the resulting metabolites possessed significant estrogenic activity at the concentrations produced. These results demonstrate the suitability of this method to degrade both sunscreen agents and to eliminate estrogenic activity.

http://www.ncbi.nlm.nih.gov/pubmed/22542301

Journal Of Pediatric Nursing • August 2012

Prevention of vector transmitted diseases with clove oil insect repellent

Author information

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Abstract

“Vector repellent is one element in the prevention of vector-borne diseases. Families that neglect protecting their children against vectors risk their children contracting illnesses such as West Nile virus, eastern equine encephalitis, Lyme disease, malaria, dengue hemorrhagic fever, yellow fever, babesiosis, Crimean-Congo hemorrhagic fever, Rocky Mountain spotted fever, Southern tick-associated rash illness, ehrlichiosis, tick-borne relapsing fever, tularemia, and other insect and arthropod related diseases (CDC, 2011). Identification of families at risk includes screening of the underlying basis for reluctance to apply insect repellent. Nurses and physicians can participate in a positive role by assisting families to determine the proper prophylaxis by recommending insect repellent choices that are economical, safe, and easy to use. A holistic alternative might include the suggestion of clove oil in cases where families might have trepidations regarding the use of DEET on children. This article will explore the safety and effectiveness of clove oil and its use as an insect repellent.”

http://www.ncbi.nlm.nih.gov/pubmed/22703681

“Thus, consistent with recent findings in humans and animals, organophosphate exposure causes dysregulation in the motor/reward circuitry and invokes mechanisms associated with neurological disorders and neurodegeneration.”

Journal Of Neurochemistry • October 2011

Organophosphates dysregulate dopamine signaling, glutamatergic neurotransmission, and induce neuronal injury markers in striatum

Author information

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Abstract

The neurological effects of organophosphate (OP) pesticides, commonly used on foods and in households, are an important public health concern. Furthermore, subclinical exposure to combinations of organophosphates is implicated in Gulf War illness. Here, we characterized the effects of the broadly used insecticide chlorpyrifos (CPF) on dopamine and glutamatergic neurotransmission effectors in corticostriatal motor/reward circuitry. CPF potentiated protein kinase A (PKA)-dependent phosphorylation of the striatal protein dopamine- and cAMP-regulated phosphoprotein of M(r) 32 kDa (DARPP-32) and the glutamate receptor 1 (GluR1) subunit of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in mouse brain slices. It also increased GluR1 phosphorylation by PKA when administered systemically. This correlated with enhanced glutamate release from cortical projections in rat striatum. Similar effects were induced by the sarin congener, diisopropyl fluorophosphate, alone or in combination with the putative neuroprotectant, pyridostigmine bromide and the pesticide N,N-diethyl-meta-toluamide (DEET). This combination, meant to mimic the neurotoxicant exposure encountered by veterans of the 1991 Persian Gulf War, also induced hyperphosphorylation of the neurofibrillary tangle-associated protein tau. Diisopropyl fluorophosphate and pyrodostigmine bromide, alone or in combination, also increased the aberrant activity of the protein kinase, Cdk5, as indicated by conversion of its activating cofactor p35 to p25. Thus, consistent with recent findings in humans and animals, organophosphate exposure causes dysregulation in the motor/reward circuitry and invokes mechanisms associated with neurological disorders and neurodegeneration.

Full text, graphs, charts and 55 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3188672/

“CONCLUSION: These findings question the safety of deet, particularly in combination with other chemicals, and they highlight the importance of a multidisciplinary approach to the development of safer insect repellents for use in public health.”

BMC Biology • August 2009

Evidence for inhibition of cholinesterases in insect and mammalian nervous systems by the insect repellent deet

Author information

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Abstract

BACKGROUND

N,N-Diethyl-3-methylbenzamide (deet) remains the gold standard for insect repellents. About 200 million people use it every year and over 8 billion doses have been applied over the past 50 years. Despite the widespread and increased interest in the use of deet in public health programmes, controversies remain concerning both the identification of its target sites at the olfactory system and its mechanism of toxicity in insects, mammals and humans. Here, we investigated the molecular target site for deet and the consequences of its interactions with carbamate insecticides on the cholinergic system.

RESULTS

By using toxicological, biochemical and electrophysiological techniques, we show that deet is not simply a behaviour-modifying chemical but that it also inhibits cholinesterase activity, in both insect and mammalian neuronal preparations. Deet is commonly used in combination with insecticides and we show that deet has the capacity to strengthen the toxicity of carbamates, a class of insecticides known to block acetylcholinesterase.

http://www.ncbi.nlm.nih.gov/pubmed/19656357

The Science Of The Total Environment • June 2006

Risk assessment of combined photogenotoxic effects of sunlight and food additives

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Abstract

“The presence of flavored colorants (peach and raspberry), flavors (caramel, citric acid and vanilla) and food preservatives (sodium nitrite, sodium nitrate, sodium benzoate, benzoic acid, potassium sorbate and sodium chloride) in Escherichia coli suspension during exposure to sunlight did not change the extent of cell survival. No effect on viability and mutation induction (kanamycin resistant) was also seen when cells were kept in contact with any of the additives for 80 min in the dark. However, when the relevant additive was present in cell suspension during sunlight exposure the number of induced mutations was increased to varying extents over that seen with sunlight alone. Raspberry and peach increased the number of mutations in a dose dependent manner, while vanilla produced mutations in an additive fashion. Nitrite, nitrate, benzoate, sorbate and benzoic acid increased mutation somewhat additively over that of sunlight. Sodium chloride and citric acid were not effective. The impact of this investigation reflects the significance of combination of sunlight and chemical food additives as potential risk, which requires special attention and necessitates further investigations to evaluate the risk.”

http://www.ncbi.nlm.nih.gov/pubmed/15979691

Neurotoxicology • July 2006

The return of the dark neuron
A histological artifact complicating contemporary neurotoxicologic evaluation

Author information

By B.S. Jortner
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Abstract

"A common histological artifact of brain is the presence of contracted, intensely stained neurons. Such cells are termed dark neurons, and can be produced by post-mortem manipulation or trauma in brain tissue. In a number of recently published experimental neurotoxicology reports cells of this nature are interpreted as representing dying or degenerating neurons, thus assigning inappropriate neurotoxic potential to the compounds administered. The latter are the commonly used drugs and pesticides DEET (N,N-diethyl m-toluamide), malathion, permethrin and pyridostigmine bromide. In this paper I review the nature and genesis of the dark neuron, critically discuss the neuropathologic validity of indicated studies and make a plea for increased awareness of this common artifact."

http://www.ncbi.nlm.nih.gov/pubmed/16650476

“Penetration of DEET in repellent spray and repellent lotion increased by 1640% and 282%, respectively, when sunscreen lotion was applied concurrently. Permeation of oxybenzone was 189% and 280% higher in repellent spray + sunscreen lotion and repellent lotion + sunscreen lotion ...”

British Journal Of Dermatology • June 2005

In vitro evaluation of concurrent use of commercially available insect repellent and sunscreen preparations

Author information

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Abstract

BACKGROUND

Insect repellents and sunscreens are over-the-counter products extensively used by the general public. Concurrent application of these products has become widespread in many regions across North America, because of concerns about West Nile virus and skin cancers.

OBJECTIVES

We investigated whether formulation type, application amount, and sequence would affect the percutaneous absorption profiles of the active repellent and sunscreen ingredients.

METHODS

In vitro percutaneous permeation of the repellent N,N-diethyl-m-toluamide (DEET) and the sunscreen oxybenzone from concurrent application of five commercially available products (A, repellent spray; B, repellent lotion; C, sunscreen lotion; D and E, combined repellent/sunscreen lotions) was measured and compared using Franz-style diffusion cells with piglet skin at 37 degrees C.

RESULTS

Penetration of DEET in A and B increased by 1640% and 282%, respectively, when C was applied concurrently. Penetration of DEET in D and E was 53% and 79% higher than that in B. Permeation of DEET from A + C (2:1) and A + C (1: 2) increased by 530% and 278%, respectively. Permeation of oxybenzone was 189% and 280% higher in A + C and B + C than in C. Permeation of oxybenzone in D and E was also 221% and 296% higher than that in C. Permeation of oxybenzone was 196% greater when A was applied on top of C than when C was applied on top of A, while oxybenzone in A + C (1:2) permeated 171% more than that in A + C (2:1).

CONCLUSIONS

Concurrent application of commercially available repellent and sunscreen products resulted in significant synergistic percutaneous permeation of the repellent DEET and the sunscreen oxybenzone in vitro. The percutaneous penetration profiles were dependent upon the type of formulation, application sequence and application proportion.

http://www.ncbi.nlm.nih.gov/pubmed/15948991

“Collectively, these results suggest that prolonged exposure to a combination of stress and the chemicals pyridostigmine bromide (PB), DEET, and permethrin can produce significant damage to the cerebral cortex, hippocampus, and cerebellum, even in the absence of apparent blood-brain barrier damage. As these areas of the brain are respectively important for the maintenance of motor and sensory functions, learning and memory, and gait and coordination of movements, such alterations could lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.”

Journal Of Toxicology And Environmental Health Part A • January 2004

Stress and combined exposure to low doses of pyridostigmine bromide, DEET, and permethrin produce neurochemical and neuropathological alterations in cerebral cortex, hippocampus, and cerebellum

Author information

Abdel-Rahman A1, Abou-Donia S, El-Masry E, Shetty A, Abou-Donia M.
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Abstract

Exposure to a combination of stress and low doses of the chemicals pyridostigmine bromide (PB), DEET, and permethrin in adult rats, a model of Gulf War exposure, produces blood-brain barrier (BBB) disruption and neuronal cell death in the cingulate cortex, dentate gyrus, thalamus, and hypothalamus. In this study, neuropathological alterations in other areas of the brain where no apparent BBB disruption was observed was studied following such exposure. Animals exposed to both stress and chemical exhibited decreased brain acetylcholinesterase (AChE) activity in the midbrain, brainstem, and cerebellum and decreased m2 muscarinic acetylcholine (ACh) receptor ligand binding in the midbrain and cerebellum. These alterations were associated with significant neuronal cell death, reduced microtubule-associated protein (MAP-2) expression, and increased glial fibrillary acidic protein (GFAP) expression in the cerebral cortex and the hippocampal subfields CA1 and CA3. In the cerebellum, the neurochemical alterations were associated with Purkinje cell loss and increased GFAP immunoreactivity in the white matter. However, animals subjected to either stress or chemicals alone did not show any of these changes in comparison to vehicle-treated controls. Collectively, these results suggest that prolonged exposure to a combination of stress and the chemicals PB, DEET, and permethrin can produce significant damage to the cerebral cortex, hippocampus, and cerebellum, even in the absence of apparent BBB damage. As these areas of the brain are respectively important for the maintenance of motor and sensory functions, learning and memory, and gait and coordination of movements, such alterations could lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.

http://www.ncbi.nlm.nih.gov/pubmed/14675905

Journal Of Toxicology And Environmental Health Part A • February 2004

Neurological deficits induced by malathion, DEET, and permethrin, alone or in combination in adult rats

Author information

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Abstract

"Malathion (O,O-dimethyl-S-[1,2-carbethoxyethyl]phosphorodithionate), DEET (N,N-diethyl-m-toluamide), and permethrin [(+/-)-cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid (3-phenoxyphenyl) methyl ester] are commonly used pesticides. To determine the effects of the dermal application of these chemicals, alone or in combination, the sensorimotor behavior, central cholinergic system, and histopathological alterations were studied in adult male Sprague-Dawley rats following a daily dermal dose of 44.4 mg/kg malathion, 40 mg/kg DEET, and 0.13 mg/kg permethrin, alone and in combination for 30 d. Neurobehavioral evaluations of sensorimotor functions included beam-walking score, beam walk time, inclined plane, and grip response assessments. Twenty-four hours after the last treatment with each chemical alone or in combination all behavioral measures were impaired. The combination of DEET and permethrin, malathion and permethrin, or the three chemicals together resulted in greater impairments in inclined performance than permethrin alone. Only animals treated with a combination of DEET and malathion or with DEET and permethrin exhibited significant increases in plasma butyrlcholinesterase (BChE) activity. Treatment with DEET or permethrin alone, malathion and permethrin, or DEET and permethrin produced significant increases in cortical acetylcholinesterase (AChE) activity. Combinations of malathion and permethrin or of DEET and permethrin produced significant decreases in midbrain AChE activity. Animals treated with DEET alone exhibited a significant increase in cortical m2 muscarinic ACh receptor binding. Quantification of neuron density in the dentate gyrus, CA1 and CA3 subfields of the hippocampus, midbrain, brainstem, and cerebellum revealed significant reductions in the density of surviving neurons with various treatments. These results suggest that **exposure to real-life doses of malathion, DEET, and permethrin, alone or in combination**, produce no **overt** signs of neurotoxicity but induce **significant neurobehavioral deficits and neuronal degeneration in brain**."

http://www.ncbi.nlm.nih.gov/pubmed/14713564

“These results suggest that exposure to various doses of pyridostigmine bromide (PB), alone and in combination with DEET and permethrin, leads to sensorimotor deficits and differential alterations of the cholinergic system in the Central Nervous System.”

Pharmacology, Biochemistry And Behavior • February 2004

Co-exposure to pyridostigmine bromide, DEET, and/or permethrin causes sensorimotor deficit and alterations in brain acetylcholinesterase activity

Author information

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Abstract

Military personnel deployed in the Persian Gulf War (PGW) were exposed to a combination of chemicals, including pyridostigmine bromide (PB), DEET, and permethrin. We investigated the dose-response effects of these chemicals, alone or in combination, on the sensorimotor performance and cholinergic system of male Sprague-Dawley rats. Animals were treated with a daily dermal dose of DEET and/or permethrin for 60 days and/or PB (gavage) during the last 15 days. Neurobehavioral performance was assessed on day 60 following the beginning of the treatment with DEET and permethrin. The rats were sacrificed 24 h after the last treatment for biochemical evaluations. PB alone, or in combination with DEET, or DEET and permethrin resulted in deficits in beam-walk score and longer beam-walk times compared to controls. PB alone, or in combination with DEET, permethrin, or DEET and permethrin caused impairment in incline plane performance and forepaw grip strength. PB alone at all doses slightly inhibited plasma butyrylcholinesterase activity, whereas combination of PB with DEET or permethrin increased its activity. Brainstem acetylcholinesterase (AChE) activity significantly increased following treatment with combinations of either DEET or permethrin at all doses, whereas the cerebellum showed a significant increase in AChE activity following treatment with a combination of PB/DEET/permethrin. Co-exposure to PB, DEET, and permethrin resulted in significant inhibition in AChE in midbrain. PB alone or in combination with DEET and permethrin at all doses increased ligand binding for m2 muscarinic acetylcholine receptor in the cortex. In addition, PB and DEET together or a combination of PB, DEET, and permethrin significantly increased ligand binding for nicotinic acetylcholine receptor. These results suggest that exposure to various doses of PB, alone and in combination with DEET and permethrin, leads to sensorimotor deficits and differential alterations of the cholinergic system in the CNS.

http://www.ncbi.nlm.nih.gov/pubmed/14751452

“Permethrin and DEET are concurrently used for pests control inside homes, in public places, and in military shelters. Combined exposure to these compounds produced greater biochemical, behavioral, and metabolic alterations in animals compared to each individual compound.”

Journal Of Toxicology And Environmental Health • Part B • Critical Reviews • January 2003

Combined exposure to DEET (N,N-diethyl-m-toluamide) and permethrin: pharmacokinetics and toxicological effects

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Abstract

Permethrin and DEET are concurrently used for pests control inside homes, in public places, and in military shelters. Combined exposure to these compounds produced greater biochemical, behavioral, and metabolic alterations in animals compared to each individual compound. Concurrent application of DEET and permethrin induced urinary excretion of 3-nitrotyrosine and 8-hydroxy-2’-deoxyguanosine, markers of DNA damage and oxidative stress in rats, increased the release of rat brain mitochondrial cytochrome c, disrupted the blood-brain barrier (BBB) in rats, decreased m2 muscarinic acetylcholine receptor ligand binding density in rat brain, increased urinary excretion of 6 beta-hydroxycortisol, a marker CYP3A4 induction, altered sensorimotor and locomotor activities in rats, and changed in vivo and in vitro metabolism and pharmacokinetic profiles of the individual compound. These findings show that more research is needed to examine adverse effects of the combined use of DEET and permethrin on other biochemical/physiological system(s) and to predict mechanistic pathways for these effects, particularly mechanism of action at cellular and molecular levels and alterations of genes transcription.

http://www.ncbi.nlm.nih.gov/pubmed/12587253

European Archives In Otorhinolaryngology • March 2002

Genotoxicity studies on permethrin, DEET and diazinon in primary human nasal mucosal cells

Author information

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Abstract

“Possible genotoxic effects exerted by three widely used pesticides, permethrin, N,N-diethyl-m-toluamide (DEET) and diazinon, in primary human nasal mucosal cells were investigated. Primary nasal mucosa cells were prepared from tissue biopsies taken from 21 patients who underwent nasal surgery. Cells were exposed to 0.5-1.0 mM concentrations of permethrin, DEET and diazinon for 60 min. Genotoxic effects were detected by the alkaline microgel electrophoresis assay (“comet assay”). Within the concentration range, no significant cytotoxic effects were observed, but **all three tested pesticides showed a significant genotoxic response that was concentration dependent. More pronounced genotoxic effects were observed in mucosal cells from the middle turbinate than in the inferior turbinate. The results provide some evidence for the potential carcinogenicity of these agents to human nasal mucosal cells.** This should be further investigated.”

http://www.ncbi.nlm.nih.gov/pubmed/12003267

International Journal Of Toxicology • September 2002

Human Exposures to N,N-diethyl-m-toluamide insect repellents reported to the American Association of Poison Control Centers 1993-1997

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Abstract

"This study analyzed 20,764 exposures involving insect repellants containing N,N-diethyl-m-toluamide (DEET) that were reported to poison control centers from 1993 to 1997. Nearly 70% of the cases reported no symptoms related to the exposure. The occurrence of symptoms was related to the route of exposure, with the highest rates associated with ocular exposures, followed by inhalation, multiple exposure routes, dermal, and ingestion. **Two deaths were reported, one in a 26-year-old male and one in a 34-year-old female, both following a dermal exposure. Twenty-six subjects experienced major effects.** The greatest number of reported exposures involved infants and children, but this group experienced lower rates of adverse effects than teens or adults. There was no clear relationship between DEET concentration and presence or severity of clinical effects. For the cases reported to poison control centers and included in this analysis, the risk of serious medical effects for labeled use of insect repellants containing N,N-diethyl-m-toluamide appears to be low."

http://www.ncbi.nlm.nih.gov/pubmed/12396679

“Data of this case analysis suggest that repellents containing DEET are not safe when applied to children’s skin and should be avoided in children. Additionally, since the potential toxicity of DEET is high, less toxic preparations should be probably substituted for DEET-containing repellents, whenever possible.”

Human Experimental Toxicology • January 2001

Toxic encephalopathy associated with use of DEET insect repellents: a case analysis of its toxicity in children

Author information

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Abstract

(1) Respiratory distress and seizures developed in an 18-month-old boy following brief exposure to low-strength (17.6%) N,N-diethyl-m-toluamide (DEET). A review of the literature revealed 17 reports of DEET-induced encephalopathy in children. The objective of this study was to test the hypothesis that the potential toxicity of DEET is high and that available repellents containing DEET, irrespective of their strength, are not safe when applied to children’s skin. (2) Although this is a case report, we used the features of published reports of DEET-induced encephalopathy in children to support the diagnosis, since the evidence that the child’s illness was caused by DEET was circumstantial. In the following case analysis, clinical reports of children < 16 years old have been reviewed and analyzed in an effort to relate direct DEET toxicity to various clinical, demographic, and toxic compound exposure factors (Fisher’s exacttest and logistic regression analysis). (3) DEET-induced encephalopathy in children (56% girls) followed not only ingestion or repeated and extensive application of repellents, but also a brief exposure to DEET (45%). Of those who reported a dermal exposure, 33% reported an exposure to a product containing DEET < 20%. Seizures, the most prominent symptom (72%), were significantly more frequent when DEET solutions were applied to the skin ($P<0.01$). Mortality (16.6%) did not correlate significantly with the concentration of the DEET liquid used, duration of skin exposure, pattern of use, age, or sex. (4) Data of this case analysis suggest that repellents containing DEET are not safe when applied to children’s skin and should be avoided in children. Additionally, since the potential toxicity of DEET is high, less toxic preparations should be probably substituted for DEET-containing repellents, whenever possible.

http://www.ncbi.nlm.nih.gov/pubmed/11339626

Toxicology Science • April 2001

Locomotor and sensorimotor performance deficit in rats following exposure to pyridostigmine bromide, DEET, and permethrin, alone and in combination

Author information

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Abstract

Since their return from Persian Gulf War (PGW), many veterans have complained of symptoms including muscle and joint pain, ataxia, chronic fatigue, headache, and difficulty with concentration. The causes of the symptoms remain unknown. Because these veterans were exposed to a combination of chemicals including pyridostigmine bromide (PB), DEET, and permethrin, we investigated the effects of these agents, alone and in combination, on the sensorimotor behavior and central cholinergic system of rats. Male Sprague-Dawley rats (200-250 gm) were treated with DEET (40 mg/kg, dermal) or permethrin (0.13 mg/kg, dermal), alone and in combination with PB (1.3 mg/kg, oral, last 15 days only), for 45 days. Sensorimotor ability was assessed by a battery of behavioral tests that included beam-walk score, beam-walk time, incline plane performance, and forepaw grip on days 30 and 45 following the treatment. On day 45 the animals were sacrificed, and plasma and CNS cholinesterase, and brain choline acetyl transferase, muscarinic and nicotinic acetylcholine receptors were evaluated. Animals treated with PB, alone or in combination with DEET and permethrin, showed a significant deficit in beam-walk score as well as beam-walk time as compared with controls. Treatment with either DEET or permethrin, alone or in combination with each other, did not have a significant effect on beam-walk score. All chemicals, alone or in combination, resulted in a significant impairment in incline plane testing on days 30 and 45 following treatment. Treatment with PB, DEET, or permethrin alone did not have any inhibitory effect on plasma or brain cholinesterase activities, except that PB alone caused moderate inhibition in midbrain acetylcholinesterase (AChE) activity. Treatment with permethrin alone caused significant increase in cortical and cerebellar AChE activity. A combination of DEET and permethrin or PB and DEET led to significant decrease in AChE activity in brainstem and midbrain and brainstem, respectively. A significant decrease in brainstem AChE activity was observed following combined exposure to PB and permethrin. Coexposure with PB, DEET, and permethrin resulted in significant inhibition in AChE in brainstem and midbrain. No effect was observed on choline acetyl transferase activity in brainstem or cortex, except combined exposure to PB, DEET, and permethrin caused a slight but significant increase in cortical choline acetyltransferase activity. Treatment with PB, DEET, and permethrin alone caused a significant increase in ligand binding for m2 muscarinic acetylcholine receptor (mAChR) in the cortex. Coexposure to PB, DEET, and permethrin did not have any effect over that of PB-induced increase in ligand binding. There was no significant change in ligand binding for nicotinic acetylcholine receptor (nAChR) associated with treatment with the chemical alone; a combination of PB and DEET or coexposure with PB, DEET, and permethrin caused a significant increase in nAChR ligand binding in the cortex. Thus, these results suggest that exposure to physiologically relevant doses of PB, DEET, and permethrin, alone or in combination, leads to neurobehavioral deficits and region-specific alterations in AChE and acetylcholine receptors.

http://www.ncbi.nlm.nih.gov/pubmed/11248143

“Thus, subchronic dermal application of DEET and permethrin to adult rats, alone or in combination, leads to a diffuse neuronal cell death in the cerebral cortex, the hippocampal formation, and the cerebellum. Collectively, the above alterations can lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.”

Experimental Neurology • November 2001

Subchronic dermal application of N,N-diethyl m-toluamide (DEET) and permethrin to adult rats, alone or in combination, causes diffuse neuronal cell death and cytoskeletal abnormalities in the cerebral cortex and the hippocampus, and Purkinje neuron loss in the cerebellum

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Abstract

N,N-Diethyl m-toluamide (DEET) and permethrin have been implicated as potential neurotoxic agents that may have played an important role in the development of illnesses in some veterans of the Persian Gulf War. To determine the effect of subchronic dermal application of these chemicals on the adult brain, we evaluated histopathological alterations in the brain of adult male rats following a daily dermal dose of DEET (40 mg/kg in 70% ethanol) or permethrin (0.13 mg/kg in 70% ethanol) or a combination of the two for 60 days. Control rats received a daily dermal dose of 70% ethanol for 60 days. Animals were perfused and brains were processed for morphological and histopathological analyses following the above regimen. Quantification of the density of healthy (or surviving) neurons in the motor cerebral cortex, the dentate gyrus, the CA1 and CA3 subfields of the hippocampus, and the cerebellum revealed significant reductions in all three treated groups compared with the control group. Further, animals receiving either DEET or permethrin exhibited a significant number of degenerating (eosinophilic) neurons in the above brain regions. However, degenerating neurons were infrequent in animals receiving both DEET and permethrin, suggesting that neuronal cell death occurs earlier in animals receiving combined DEET and permethrin than in animals receiving either DEET or permethrin alone. The extent of neuron loss in different brain regions was similar among the three treatment groups except the dentate gyrus, where neurodegeneration was significantly greater with exposure to DEET alone. The neuron loss in the motor cerebral cortex and the CA1 subfield of all treated groups was also corroborated by a significant decrease in microtubule associated protein 2-immunoreactive elements (15-52% reduction), with maximal reductions occurring in rats receiving DEET alone; further, the surviving neurons in animals receiving both DEET and permethrin exhibited wavy and beaded dendrites. Analysis of glial fibrillary acidic protein immunoreactivity revealed significant hypertrophy of astrocytes in the hippocampus and the cerebellum of all treated groups (24-106% increase). Thus, subchronic dermal application of DEET and permethrin to adult rats, alone or in combination, leads to a diffuse neuronal cell death in the cerebral cortex, the hippocampal formation, and the cerebellum. Collectively, the above alterations can lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.

http://www.ncbi.nlm.nih.gov/pubmed/11681848

“In effect, pyridostigmine bromide “pumps” more DEET and permethrin into the central nervous system. Consistent with this hypothesis, hens exposed to the combination of the three agents exhibited neuropathological lesions with several characteristics similar to those previously reported in studies of near-lethal doses of DEET and permethrin. If this hypothesis is correct, then blood and liver esterases play an important “buffering” role in protecting against neurotoxicity in the population at large. It also suggests that individuals with low plasma esterase activity may be predisposed to neurologic deficits produced by exposure to certain chemical mixtures.”

Journal Of Toxicology And Environmental Health • May 1996

Neurotoxicity resulting from coexposure to pyridostigmine bromide, deet, and permethrin: implications of Gulf War chemical exposures

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Abstract

Of the three-quarters of a million service personnel involved in the Persian Gulf War, approximately 30,000 have complained of neurological symptoms of unknown etiology. One contributing factor to the emergence of such symptoms may be the simultaneous exposure to multiple agents used to protect the health of service personnel, in particular, the anti-nerve agent pyridostigmine bromide (PB; 3-dimethylaminocarbonyloxy-N-methylpyridinium bromide), the insect repellent DEET (N,N-diethyl-m-toluamide), and the insecticide permethrin (3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester). This study investigated neurotoxicity produced in hens by individual or simultaneous exposure to these agents (5 d/wk for 2 months to 5 mg/kg/d PB in water, po; 500 mg/kg/d DEET, neat, sc; and 500 mg/kg/d permethrin in corn oil, sc). At these dosages, exposure to single compounds resulted in minimal toxicity. Combinations of two agents produced greater neurotoxicity than that caused by individual agents. Neurotoxicity was further enhanced following concurrent administration of all three agents. We hypothesize that competition for liver and plasma esterases by these compounds leads to their decreased breakdown and increased transport of the parent compound to nervous tissues. Thus, carbamylation of peripheral esterases by PB reduces the hydrolysis of DEET and permethrin and increases their availability to the nervous system. In effect, PB “pumps” more DEET and permethrin into the central nervous system. Consistent with this hypothesis, hens exposed to the combination of the three agents exhibited neuropathological lesions with several characteristics similar to those previously reported in studies of near-lethal doses of DEET and permethrin. If this hypothesis is correct, then blood and liver esterases play an important “buffering” role in protecting against neurotoxicity in the population at large. It also suggests that individuals with low plasma esterase activity may be predisposed to neurologic deficits produced by exposure to certain chemical mixtures.

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“Adults, as well as children, are at risk for toxicity from insect repellents. The use of highly concentrated DEET-containing insect repellents should be avoided to reduce the risk of toxicity in both children and adults. The consequences of DEET toxicity are variable and unpredictable.”

Annals In Pharmacotherapy • March 1993

Insect repellent (N,N-diethyl-m-toluamide) cardiovascular toxicity in an adult

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Abstract

OBJECTIVE

To describe a case of N,N-diethyl-m-toluamide (DEET)-induced cardiovascular toxicity in an adult and reviews other cases that have been reported in the published literature. Human and animal data available on DEET pharmacokinetics are reviewed and factors that predispose an individual to DEET toxicity are identified.

DATA SOURCES

Case report information was obtained through personal contact with the patient during hospitalization and by telephone, and also from the patient’s medical records. Computerized literature searches were conducted with the following systems to obtain medical literature on DEET toxicity: TOXLINE, International Pharmaceutical Abstracts, and MEDLINE. Index Medicus was searched manually.

STUDY SELECTION

All reported cases of DEET toxicity in children and adults were reviewed.

DATA EXTRACTION

Case reports were evaluated for the quantity of the DEET exposure (topical or oral), the clinical manifestations of the exposure, and the outcome of the exposure.

DATA SYNTHESIS

This case is similar in some aspects to those already in the literature; however, very few cases of DEET toxicity in adults have been reported. Cardiovascular toxicity in humans related to DEET application has not been previously reported in the published medical literature. DEET exposure (topical or oral) results in a highly variable clinical course. Whether the outcome is death or recovery without sequelae is difficult to predict.

CONCLUSIONS

Adults, as well as children, are at risk for toxicity from insect repellents. The use of highly concentrated DEET-containing insect repellents should be avoided to reduce the risk of toxicity in both children and adults. The consequences of DEET toxicity are variable and unpredictable.

http://www.ncbi.nlm.nih.gov/pubmed/8453162

Fundamental Applied Toxicology • July 1992

Reproductive and developmental toxicity of N,N-diethyl-m-toluamide in rats

Author information

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Abstract

"N,N-Diethyl-m-toluamide (mDET, DEET) is widely used as a topical insect repellent. It is the active ingredient in many consumer formulations, which usually contain 10-25% mDET in an alcohol base. More concentrated consumer products are also available, including some that are pure technical grade mDET. Persons living or employed in mosquito-infested areas may have very high seasonal exposures to mDET. Because contradictory reports had been published on the reproductive and developmental toxicity of mDET, a series of studies was conducted in male and female Sprague-Dawley rats. All treatments were administered by daily subcutaneous injections of undiluted mDET. A dose finding study was done using 12 time-mated females per group treated on Gestational Days (GD) 6-15 with 0.50, 0.62, 0.78, 0.92, or 1.2 ml mDET/kg/day. No females survived 10 days of mDET dosing with 1.2 ml/kg/day. Deaths occurred in all other groups except the low dose (0.50 ml/kg/day). Pregnant females treated on GD 6-15 with 0 or 0.30 ml/kg/day were used for the teratology study. Half of each group was euthanized on GD 20: the second half was singly housed in nesting boxes and allowed to deliver litters. Live pups were counted and weighed soon after birth on Postnatal Day (PD) 0 and again on PD 3, 9, and 14. Proven fertile males were treated 5 days/week for 9 weeks with 0, 0.30, 0.73, 1.15, or 1.80 ml mDET/kg/day for a male dose-finding study. Each group consisted of 20 males. No males survived the 1.80 ml/kg/day. Deaths occurred in all remaining dose groups except the 0.30 ml/kg/day and control group. Immediately following the final treatment of the male dose study, 11 males were randomly selected from the 0.30 and 0.73 ml/kg/day groups. They were cohabited for 7 days with 4 females per male during post-treatment Weeks 1 and 2. Half of the females were euthanized 12-14 days after the last day of cohabitation for a dominant lethal study; the remaining females were singly housed in nesting boxes and allowed to deliver litters. Live pups were counted and weighted on PD 0 and 3. There was no evidence of reproductive or developmental toxicity in any of these assays, **but there were signs of neurotoxicity in treated adult male and female rats, which may relate to reports of neurotoxicity in humans heavily exposed to mDET-containing [DEET-containing] insect repellents.**"

http://www.ncbi.nlm.nih.gov/pubmed/1397799

CHAPTER THIRTY-NINE

Vitamins, Nutrients & Micronutrients

The Peer Review

A vitamin is an organic compound and a vital nutrient that an organism requires in limited amounts. An organic chemical compound (or related set of compounds) is called a vitamin when the organism cannot synthesize the compound in sufficient quantities, and it must be obtained through the diet; thus, the term "vitamin" is conditional upon the circumstances and the particular organism. For example, ascorbic acid (one form of vitamin C) is a vitamin for humans, but not for most other animal organisms. Supplementation is important for the treatment of certain health problems, but there is little evidence of nutritional benefit when used by otherwise healthy people.

By convention the term vitamin includes neither other essential nutrients, such as dietary minerals, essential fatty acids, or essential amino acids (which are needed in greater amounts than vitamins) nor the great number of other nutrients that promote health, and are required less often to maintain the health of the organism. Thirteen vitamins are universally recognized at present. Vitamins are classified by their biological and chemical activity, not their structure. Thus, each "vitamin" refers to a number of vitamer compounds that all show the biological activity associated with a particular vitamin. Such a set of chemicals is grouped under an alphabetized vitamin "generic descriptor" title, such as "vitamin A", which includes the compounds retinal, retinol, and four known carotenoids. Vitamers by definition are convertible to the active form of the vitamin in the body, and are sometimes inter-convertible to one another, as well.

Vitamins have diverse biochemical functions. Some, such as vitamin D, have hormone-like functions as regulators of mineral metabolism, or regulators of cell and tissue growth and differentiation (such as some forms of vitamin A). Others function as antioxidants (e.g., vitamin E and sometimes vitamin C). The largest number of vitamins, the B complex vitamins, function as enzyme cofactors (coenzymes) or the precursors for them; coenzymes help enzymes in their work as catalysts in metabolism. In this role, vitamins may be tightly bound to enzymes as part of prosthetic groups: For example, biotin is part of enzymes involved in making fatty acids. They may also be less tightly bound to enzyme catalysts as coenzymes, detachable molecules that function to carry chemical groups or electrons between molecules. For example, folic acid may carry methyl, formyl, and methylene groups in the cell. Although these roles in assisting enzyme-substrate reactions are vitamins' best-known function, the other vitamin functions are equally important.

Until the mid-1930s, when the first commercial yeast-extract vitamin B complex and semi-synthetic vitamin C supplement tablets were sold, vitamins were obtained solely through food intake, and changes in diet (which, for example, could occur during a particular growing season) usually greatly altered the types and amounts of vitamins ingested. However, vitamins have been produced as commodity chemicals and made widely available as inexpensive semisynthetic and synthetic-source multivitamin dietary and food supplements and additives, since the middle of the 20th century. Study of structural activity, function and their role in maintaining health is called vitaminology. Vitamins are essential for the normal growth and de-

velopment of a multicellular organism. Using the genetic blueprint inherited from its parents, a fetus begins to develop, at the moment of conception, from the nutrients it absorbs. It requires certain vitamins and minerals to be present at certain times. These nutrients facilitate the chemical reactions that produce among other things, skin, bone, and muscle. If there is serious deficiency in one or more of these nutrients, a child may develop a deficiency disease. Even minor deficiencies may cause permanent damage.

For the most part, vitamins are obtained with food, but a few are obtained by other means. For example, microorganisms in the intestine — commonly known as "gut flora" — produce vitamin K and biotin, while one form of vitamin D is synthesized in the skin with the help of the natural ultraviolet wavelength of sunlight. Humans can produce some vitamins from precursors they consume. Examples include vitamin A, produced from beta carotene, and niacin, from the amino acid tryptophan.

Once growth and development are completed, vitamins remain essential nutrients for the healthy maintenance of the cells, tissues, and organs that make up a multicellular organism; they also enable a multicellular life form to efficiently use chemical energy provided by food it eats, and to help process the proteins, carbohydrates, and fats required for respiration.

In those who are otherwise healthy, there is little evidence that supplements have any benefits with respect to cancer or heart disease. Vitamin A and E supplements not only provide no health benefits for generally healthy individuals, but they may increase mortality, though the two large studies that support this conclusion included smokers for whom it was already known that beta-carotene supplements can be harmful. While other findings suggest that vitamin E toxicity is limited to only a specific form when taken in excess.

The European Union and other countries of Europe have regulations that define limits of vitamin (and mineral) dosages for their safe use as food supplements. Most vitamins that are sold as food supplements cannot exceed a maximum daily dosage. Vitamin products above these legal limits are not considered food supplements and must be registered as prescription or non-prescription (over-the-counter drugs) due to their potential side effects. As a result, most of the fat-soluble vitamins (such as the vitamins A, D, E, and K) that contain amounts above the daily allowance are drug products. The daily dosage of a vitamin supplement for example cannot exceed 300% of the recommended daily allowance, and for vitamin A, this limit is even lower (200%). Such regulations are applicable in most European countries.

Dietary supplements often contain vitamins, but may also include other ingredients, such as minerals, herbs, and botanicals. Scientific evidence supports the benefits of dietary supplements for persons with certain health conditions. In some cases, vitamin supplements may have unwanted effects, especially if taken before surgery, with other dietary supplements or medicines, or if the person taking them has certain health conditions. They may also contain levels of vitamins many times higher, and in different forms, than one may ingest through food.

Humans must consume vitamins periodically but with differing schedules, to avoid deficiency. The human body's stores for different vitamins vary widely; vitamins A, D, and B12 are stored in significant amounts in the human body, mainly in the liver, and an adult human's diet may be deficient in vitamins A and D for many months and B12 in some cases for years, before developing a deficiency condition. However, vitamin B3 (niacin and niacinamide) is not stored in the human body in significant amounts, so stores may last only a couple of weeks. For vitamin C, the first symptoms of scurvy in experimental studies of complete vitamin C deprivation in humans have varied widely, from a month to more than six months, depending on previous dietary history that determined body stores.

Deficiencies of vitamins are classified as either primary or secondary. A primary deficiency occurs when an organism does not get enough of the vitamin in its food. A secondary deficiency may be due to an underlying disorder that prevents or limits the absorption or use of the vitamin, due to a "lifestyle factor", such as smoking, excessive alcohol consumption, or the use of medications that interfere with the absorption or use of the vitamin. People who eat a varied diet are unlikely to develop a severe primary vitamin deficiency. In contrast, restrictive diets have the potential to cause prolonged vitamin deficits, which may result in often painful and potentially deadly diseases.

Well-known human vitamin deficiencies involve thiamine (beriberi), niacin (pellagra), vitamin C (scurvy), and vitamin D (rickets). In much of the developed world, such deficiencies are rare; this is due to (1) an adequate supply of food and (2) the addition of vitamins and minerals to common foods, often called fortification. In addition to these classical vitamin deficiency diseases, some evidence has also suggested links between vitamin deficiency and a number of different disorders. In large doses, some vitamins have documented side-effects that tend to be more severe with a larger dosage. The likelihood of consuming too much of any vitamin from food is remote, but overdosing (vitamin poisoning) from vitamin supplementation does occur. At high enough dosages, some vitamins cause side-effects such as nausea, diarrhea, and vomiting. When

side-effects emerge, recovery is often accomplished by reducing the dosage. The doses of vitamins differ because individual tolerances can vary widely and appear to be related to age and state of health.

In 2008, overdose exposure to all formulations of vitamins and multivitamin-mineral formulations was reported by 68,911 individuals to the American Association of Poison Control Centers (nearly 80% of these exposures were in children under the age of 6), leading to 8 "major" life-threatening outcomes, but no deaths.

The reason that the set of vitamins skips directly from E to K is that the vitamins corresponding to letters F–J were either reclassified over time, discarded as false leads, or renamed because of their relationship to vitamin B, which became a complex of vitamins.

The German-speaking scientists who isolated and described vitamin K (in addition to naming it as such) did so because the vitamin is intimately involved in the coagulation of blood following wounding (from the German word Koagulation). At the time, most (but not all) of the letters from F through to J were already designated, so the use of the letter K was considered quite reasonable. The table nomenclature of reclassified vitamins lists chemicals that had previously been classified as vitamins, as well as the earlier names of vitamins that later became part of the B-complex.

There are other missing B vitamins which were reclassified or determined not to be vitamins. For example, B9 is folic acid and five of the folates are in the range B11 through B16, forms of other vitamins already discovered, not required as a nutrient by the entire population (like B10, PABA for internal use), biologically inactive, toxic, or with unclassifiable effects in humans, or not generally recognized as vitamins by science, such as the highest-numbered, which some naturopath practitioners call B21 and B22. There are also nine lettered B complex vitamins (e.g. Bm). There are other D vitamins now recognized as other substances, which some sources of the same type number up to D7. The controversial cancer treatment laetrile was at one point lettered as vitamin B17. There appears to be no consensus on any vitamins Q, R, T, V, W, X, Y or Z, nor are there substances officially designated as Vitamins N or I, although the latter may have been another form of one of the other vitamins or a known and named nutrient of another type.

Previous name	Chemical name	Reason for name change
Vitamin B_4	Adenine	DNA metabolite; synthesized in body
Vitamin B_8	Adenylic acid	DNA metabolite; synthesized in body
Vitamin F	Essential fatty acids	Needed in large quantities (does not fit the definition of a vitamin).
Vitamin G	Riboflavin	Reclassified as Vitamin B_2
Vitamin H	Biotin	Reclassified as Vitamin B_7
Vitamin J	Catechol, Flavin	Catechol nonessential; flavin reclassified as Vitamin B_2
Vitamin L_1[60]	Anthranilic acid	Non essential
Vitamin L_2[60]	Adenylthiomethylpentose	RNA metabolite; synthesized in body
Vitamin M	Folic acid	Reclassified as Vitamin B_9
Vitamin O	Carnitine	Synthesized in body
Vitamin P	Flavonoids	No longer classified as a vitamin
Vitamin PP	Niacin	Reclassified as Vitamin B_3
Vitamin S	Salicylic acid	Proposed inclusion of salicylate as an essential micronutrient
Vitamin U	S-Methylmethionine	Protein metabolite; synthesized in body

Vitamin	Soluble in Water	Exposure to Air	Exposure to Light	Exposure to Heat
Vitamin C	very unstable	yes	yes	yes
Pantothenic Acid (B_5)	quite stable	?	no	yes
Vitamin A	no	partially	partially	relatively stable
Vitamin D	no	no	no	no
Vitamin E	no	yes	yes	no
Vitamin K	no	no	yes	no
Riboflavin (B_2)	slightly	no	in solution	no
Niacin (B_3)	yes	no	no	no
Biotin (B_7)	somewhat	?	?	no
Vitamin B_{12}	yes	?	yes	no
Folic Acid (B_9)	yes	?	when dry	at high temp
Vitamin B_6	yes	?	yes	?
Thiamine (B_1)	highly	no	?	> 100 °C

Journal Of The American Geriatric Society • January 2016

Response of Vitamin D Concentration to Vitamin D3 Administration in Older Adults without Sun Exposure: A Randomized Double-Blind Trial

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Abstract

OBJECTIVES
To determine the dose-response relationship between 25-hydroxyvitamin D (25(OH)D) and supplemental vitamin D3 in elderly nursing home residents.
DESIGN
Randomized double-blind investigation.
SETTING
Nursing home.
PARTICIPANTS
Of 81 women (n=51) and men (n=30) (mean age 87.4±8) enrolled, 72 completed the study.
INTERVENTION
Sixteen weeks of oral vitamin D3 at 800, 2,000, or 4,000 IU/d or 50,000 IU/wk.
MEASUREMENTS
The main outcome was 25(OH)D concentrations (tandem mass spectrometry) after 16 weeks. Free 25(OH)D and intact parathyroid hormone (iPTH) were also analyzed. Safety monitoring of calcium and estimated glomerular filtration rate was performed, and adherence and clinical status were measured.
RESULTS
25(OH)D concentrations increased with dose (P<.001) and were higher with 50,000 IU/wk (P<.001) than other doses and with 4,000 IU/d than 800 or 2,000 IU/d, but 800 IU and 2,000 IU/d did not differ. One subject receiving 800 IU/d had concentrations less than 20 ng/mL. All subjects receiving more than 2000 IU/d had concentrations of 20 ng/mL and greater. Free 25(OH)D concentrations rose with total 25(OH) vitamin D. Total and free 25(OH)D were related to calcium concentrations; only free 25(OH)D was related to iPTH.
CONCLUSION
25(OH)D increased linearly with 800 to 4,000 IU/d and 50,000 IU/wk of vitamin D3, without a ceiling effect. Data suggest that some elderly adults will require more than 800 IU/d of vitamin D3 to ensure adequate vitamin D levels. Changes in 25(OH)D with vitamin D3 were related to starting concentrations (greatest with the lowest concentrations and unchanged with 800 and 2,000 IU/d if 20-40 ng/mL). Relationships between serum calcium and iPTH and free 25(OH)D suggest the potential for free 25(OH)D in defining optimal 25(OH)D concentrations.

http://www.ncbi.nlm.nih.gov/pubmed/26782853

“25(OH)D increased linearly with 800 to 4,000 International Units/per day and 50,000 IU/per week of vitamin D3, without a ceiling effect.

Data suggest that some elderly adults will require more than 800 International Units/per day of vitamin D3 to ensure adequate vitamin D levels.”

“... studies utilizing mouse models of colitis have shown that vitamin D is beneficial in preventing or ameliorating inflammation and clinical disease. The precise role of vitamin D on colitis is unknown; however, vitamin D regulates immune cell trafficking and differentiation, gut barrier function and antimicrobial peptide synthesis, all of which may be protective from inflammatory bowel disease and colon cancer. Here we focus on effects of vitamin D on inflammation and inflammation-associated colon cancer and discuss the potential use of vitamin D for protection and treatment of inflammatory bowel disease and colon cancer.”

World Journal Of Gastroenterology • January 2016

Protective links between vitamin D, inflammatory bowel disease and colon cancer

Author information

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Abstract

Vitamin D deficiency has been associated with a wide range of diseases and multiple forms of cancer including breast, colon, and prostate cancers. Relatively recent work has demonstrated vitamin D to be critical in immune function and therefore important in inflammatory diseases such as inflammatory bowel disease (IBD). Because vitamin D deficiency or insufficiency is increasingly prevalent around the world, with an estimated 30%-50% of children and adults at risk for vitamin D deficiency worldwide, it could have a significant impact on IBD. Epidemiologic studies suggest that low serum vitamin D levels are a risk factor for IBD and colon cancer, and vitamin D supplementation is associated with decreased colitis disease activity and/or alleviated symptoms. Patients diagnosed with IBD have a higher incidence of colorectal cancer than the general population, which supports the notion that inflammation plays a key role in cancer development and underscores the importance of understanding how vitamin D influences inflammation and its cancer-promoting effects. In addition to human epidemiological data, studies utilizing mouse models of colitis have shown that vitamin D is beneficial in preventing or ameliorating inflammation and clinical disease. The precise role of vitamin D on colitis is unknown; however, vitamin D regulates immune cell trafficking and differentiation, gut barrier function and antimicrobial peptide synthesis, all of which may be protective from IBD and colon cancer. Here we focus on effects of vitamin D on inflammation and inflammation-associated colon cancer and discuss the potential use of vitamin D for protection and treatment of IBD and colon cancer.

Full text, graphs, charts and 145 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4716046/

British Journal Of Nutrition • January 2016

Prenatal folate, homocysteine and vitamin B12 levels and child brain volumes, cognitive development and psychological functioning: the Generation R Study

Author information

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Abstract

“Previous studies have suggested that prenatal maternal folate deficiency is associated with reduced prenatal brain growth and psychological problems in offspring. However, little is known about the longer-term impact. The aims of this study were to investigate whether prenatal maternal folate insufficiency, high total homocysteine levels and low vitamin B12 levels are associated with altered brain morphology, cognitive and/or psychological problems in school-aged children. This study was embedded in Generation R, a prospective population-based cohort study. The study sample consisted of 256 Dutch children aged between 6 and 8 years from whom structural brain scans were collected using MRI. The mothers of sixty-two children had insufficient (9·1 μmol/l) predicted poorer performance on the language (B -0·31; 95 % CI -0·56, -0·06; P=0·014) and visuo-spatial domains (B -0·36; 95 % CI -0·60, -0·11; P=0·004). No associations with psychological problems were found. Our findings suggest that folate insufficiency in early pregnancy has a long-lasting, global effect on brain development and is, together with homocysteine levels, associated with poorer cognitive performance.”

http://www.ncbi.nlm.nih.gov/pubmed/26794411

Ugeskrift For Laeger • January 2016

Vegetarians are at high risk of vitamin B12 deficiency

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Abstract

“Since vegetarians have a lower intake of vitamin B12 (B12) than non-vegetarians, they are at increased risk of developing B12 deficiency. The less animal products the food contains the worse the B12 status. However, even lacto-ovo-vegetarians run the risk of becoming deficient in B12. Vegetarians are recommended regularly to take supplements of B12, and they should be informed of the lacking content of B12 of plant products and the hazards of B12 deficiency. Furthermore, vegetarians should routinely be checked for possible B12 deficiency.”

http://www.ncbi.nlm.nih.gov/pubmed/26750191

Critical Reviews In Food Science Nutrition • January 2016

Association between Vitamin Deficiency and Metabolic Disorders Related to Obesity

Author information

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Abstract

"Inappropriate food behavior contributes to obesity and leads to vitamin deficiency. This review discusses the nutritional status of water- and fat-soluble vitamins in obese subjects. We verified that most vitamins are deficient in obese individuals, especially the fat-soluble vitamins, folic acid, vitamin B12 and vitamin C. However, some vitamins have been less evaluated in cases of obesity. The adipose tissue is considered a metabolic and endocrine organ, which in excess leads to changes in body homeostasis, as well as vitamin deficiency which can aggravate the pathological state. Therefore, the evaluation of vitamin status is of fundamental importance in obese individuals."

http://www.ncbi.nlm.nih.gov/pubmed/26745150

“... the data also suggest that treatment effects were more pronounced in younger children with Autism Spectrum Disorder. Vitamin D deficiency might contribute to the aetiology of Autism Spectrum Disorder. Supplementation of vitamin D3, which is a safe and cost-effective form of treatment, may significantly improve the outcome of some children with Autism Spectrum Disorder, especially younger children ...”

Nutrition And Neuroscience • January 2016

Clinical improvement following vitamin D3 supplementation in Autism Spectrum Disorder

Feng J, Shan L, Du L, Wang B, Li H, Wang W, Wang T, Dong H, Yue X, Xu Z, Staal WG, Jia F.

Abstract

Objective High prevalence of vitamin D deficiency was previously reported in children with Autism Spectrum Disorder (ASD), but little is known about the efficacy of vitamin D3 treatment in ASD, although data from pilot studies seem promising. We hypothesized that serum vitamin D levels are reduced in ASD and correlate with the severity of disease. Also, we hypothesized that vitamin D3 treatment may be beneficial for a considerable portion of children with ASD. Methods In total, 215 children with ASD and 285 healthy control children were recruited in our study. Thirty seven of 215 ASD children received vitamin D3 treatment. The Autism Behaviour Checklist (ABC) and the Childhood Autism Rating Scale (CARS) were used to assess autism symptoms. High-performance liquid chromatography was used to assess the serum 25-hydroxyvitamin D [25(OH) D] level. Evaluations of ABC, CARS, and serum 25(OH) D levels were performed before and after 3 months of treatment. Results Serum levels of 25(OH) D were significantly lower in ASD children than typically developing children. Levels of serum 25(OH) D were negatively correlated with ABC total scores and language subscale scores. After vitamin D3 supplementation, symptom scores were significantly reduced on the CARS and ABC. In addition, the data also suggest that treatment effects were more pronounced in younger children with ASD. Conclusion Vitamin D deficiency might contribute to the aetiology of ASD. Supplementation of vitamin D3, which is a safe and cost-effective form of treatment, may significantly improve the outcome of some children with ASD, especially younger children (identifier ChiCTR-CCC-13004498). Clinical Trial Registration The trial ‘Association of Polymorphisms of Vitamin D Metabolism-Related Genes With Autism and the Treatment of Autism with Vitamin D’ has been registered at www.chictr.org/cn/proj/show.aspx ? proj=6135 (identifier ChiCTR-CCC-13004498).

http://www.ncbi.nlm.nih.gov/pubmed/26783092

“Thus our findings reveal a previously unrecognized decrease in brain vitamin B12 status across the lifespan that may reflect an adaptation to increasing antioxidant demand, while accelerated deficits due to GSH deficiency may contribute to neurodevelopmental and neuropsychiatric disorders.”

PLoS One • January 2016

Decreased Brain Levels of Vitamin B12 in Aging, Autism and Schizophrenia

Author information

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Abstract

Many studies indicate a crucial role for the vitamin B12 and folate-dependent enzyme methionine synthase (MS) in brain development and function, but vitamin B12 status in the brain across the lifespan has not been previously investigated. Vitamin B12 (cobalamin, Cbl) exists in multiple forms, including methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl), serving as cofactors for MS and methylmalonylCoA mutase, respectively. We measured levels of five Cbl species in postmortem human frontal cortex of 43 control subjects, from 19 weeks of fetal development through 80 years of age, and 12 autistic and 9 schizophrenic subjects. Total Cbl was significantly lower in older control subjects (> 60 yrs of age), primarily reflecting a >10-fold age-dependent decline in the level of MeCbl. Levels of inactive cyanocobalamin (CNCbl) were remarkably higher in fetal brain samples. In both autistic and schizophrenic subjects MeCbl and AdoCbl levels were more than 3-fold lower than age-matched controls. In autistic subjects lower MeCbl was associated with decreased MS activity and elevated levels of its substrate homocysteine (HCY). Low levels of the antioxidant glutathione (GSH) have been linked to both autism and schizophrenia, and both total Cbl and MeCbl levels were decreased in glutamate-cysteine ligase modulatory subunit knockout (GCLM-KO) mice, which exhibit low GSH levels. Thus our findings reveal a previously unrecognized decrease in brain vitamin B12 status across the lifespan that may reflect an adaptation to increasing antioxidant demand, while accelerated deficits due to GSH deficiency may contribute to neurodevelopmental and neuropsychiatric disorders.

Full text with 90 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723262/

“Vitamin D deficiency was prevalent among South Asian, Middle Eastern and African women. The serum levels of 25(OH)D increased significantly from GW 15 to 28 in vitamin D deficient women who received a recommendation for supplementation. This recommendation of vitamin D supplementation increased vitamin D levels in deficient women.”

BMC Pregnancy And Childbirth • January 2016

Vitamin D deficiency and supplementation in pregnancy in a multiethnic population-based cohort

Author information

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Abstract

BACKGROUND

To investigate ethnic differences in vitamin D levels during pregnancy, assess risk factors for vitamin D deficiency and explore the effect of vitamin D supplementation in women with deficiency in early pregnancy.

METHODS

This is a population-based, multiethnic cohort study of pregnant women attending Child Health Clinics for antenatal care in Oslo, Norway. Serum-25-hydroxyvitamin D [25(OH)D] was measured in 748 pregnant women (59% ethnic minorities) at gestational weeks (GW) 15 (SD:3.6) and 28 (1.4). Women with 25(OH)D <37 nmol/L at GW 15 were for ethical reasons recommended vitamin D3 supplementation. Main outcome measure was 25(OH)D, and linear regression models were performed.

RESULTS

Severe deficiency (25(OH)D <25 nmol/L) was found at GW 15 in 45% of women from South Asia, 40% from the Middle East and 26% from Sub-Saharan Africa, compared to 2.5% in women from East Asia and 1.3% of women from Western Europe. Women from South Asia, the Middle East and Sub-Saharan Africa had mean values that were -28 (95 % CI:-33, -23), -24 (-29, -18) and -20 (-27, -13) nmol/L lower than in Western women, respectively. Ethnicity, education, season and intake of vitamin D were independently associated with 25(OH)D. At GW 28, the mean 25(OH)D had increased from 23 (SD:7.8) to 47 (27) nmol/L ($p < 0.01$) in women who were recommended vitamin D supplementation, with small or no change in women with sufficient vitamin D levels at baseline.

CONCLUSIONS

Vitamin D deficiency was prevalent among South Asian, Middle Eastern and African women. The serum levels of 25(OH)D increased significantly from GW 15 to 28 in vitamin D deficient women who received a recommendation for supplementation. This recommendation of vitamin D supplementation increased vitamin D levels in deficient women.

Full text, graphs, charts and 47 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4719746/

Journal AOAC International • January 2016

Determination of Vitamin E and Vitamin A in Infant Formula and Adult Nutritionals by Normal-Phase High-Performance Liquid Chromatography: Collaborative Study, Final Action 2012.10.

Author information

Wyeth

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Abstract

"The main objective of the AOAC Stakeholder Panel on Infant Formula and Adult Nutritionals (SPIFAN) project is to establish international consensus methods for infant formula and adult nutritionals, which will benefit intermarket supply and dispute resolution. A collaborative study was conducted on AOAC First Action Method 2012.10 Simultaneous Determination of 13-cis and All-trans Vitamin A Palmitate (Retinyl Palmitate), Vitamin A Acetate (Retinyl Acetate), and Total Vitamin E (ß-Tocopherol and D-ß-tocopherol acetate) in Infant Formula and Adult Nutritionals by Normal-Phase HPLC. Fifteen laboratories from 11 countries participated in an interlaboratory study to determine 13-cis and all-trans vitamin A palmitate (retinyl palmitate), vitamin A acetate (retinyl acetate), and total vitamin E (ß-tocopherol and D-ß-tocopherol acetate) in infant formula and adult nutritionals by normal-phase HPLC and all laboratories returned valid data. Eighteen test portions of nine blind duplicates of a variety of infant formula and adult nutritional products were used in the study. The matrixes included milk-based and soy-based hydrolyzed protein as well as a low fat product. Each of the samples was prepared fresh and analyzed in singlicate. As the number of samples exceeded the recommended number to be prepared in a single day, analysis took place over 2 days running 12 samples on day one and 10 samples on day two. The reference standard stock was prepared once and the six-point curve diluted freshly on each day. Results obtained from all 15 laboratories are reported. The RSDR for total vitamin A (palmitate or acetate) ranged from 6.51 to 22.61% and HorRat values ranged from 0.33 to 1.25. The RSDR for total vitamin E (as tocopherol equivalents) ranged from 3.84 to 10.78% and HorRat values ranged from 0.27 to 1.04. Except for an adult low fat matrix which generated reproducibility RSD >40% for some isomers, most SPIFAN matrixes gave results within the acceptance criteria of <16% RSD as stated in the respective Standard Method Performance Requirements."

http://www.ncbi.nlm.nih.gov/pubmed/26856624

JPEN Journal Of Parenteral And Enteral Nutrition • January 2016

Use of a Loading Dose of Vitamin D for Treatment of Vitamin D Deficiency in Patients With Intestinal Failure

Author information

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Abstract

“Vitamin D deficiency is common in patients with intestinal failure and short bowel syndrome who have been weaned of parenteral nutrition. Dietary supplementation with vitamin D is necessary to correct this deficiency. In certain cases, routine supplementation strategy may be ineffective. We report 3 cases of vitamin D deficiency in patients with intestinal failure who showed improvement in serum 25-hydroxyvitamin D levels after supplementation with a loading dose of 20,000-40,000 IU vitamin D provided weekly.”

http://www.ncbi.nlm.nih.gov/pubmed/26826260

Journal Of Nutrition, Health And Aging • January 2016

Hyperhomocysteinemia Is Associated with Vitamin B-12 Deficiency: A Cross-sectional Study in a Rural, Elderly Population of Shanxi China

Author information

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Abstract

OBJECTIVES

To report the association of lifestyle factors and plasma vitamin B-12 with hyperhomocysteinemia in a large sample of men and women living in a region of China where there is an increased risk of NTDs.

DESIGN

Community-based, cross-sectional study of Lvliang City, Shanxi Province, China.

SETTING

Hyperhomocysteinemia is an independent risk factor for cardiovascular disease (CVD) and a sensitive marker of vitamin B-12 and folate deficiency.

PARTICIPANTS

A total of 2355 (1044 men and 1311 women) participants born before 1 January 1958 (≥55 years of age) and living in Lvliang City for at least 2 months a year were included.

MEASUREMENTS

The participants were assessed regarding demographic characteristics, height, weight, as well as having a physical examination and blood sampling for serum cholesterol, total homocysteine (tHcy), folate, and vitamin B12 levels.

RESULTS

The median (25th-75th percentile) tHcy concentration was 21.5 (15.8-33.6) μmol/L in men and 18.0 (13.4-24.8) μmol/L in women. The overall prevalence of hyperhomocysteinemia (tHcy ≥15 μmol/L) was 72.6% (84.3% in men and 63.2% in women), inversely correlated with folate (r=-0.230, P=0.006) and vitamin B-12 (r=-0.540, P<0.001), and positively correlated with uric acid (r=0.054, P<0.001). Vitamin B-12 and folate deficiency, older age, and male gender were associated with elevated tHcy; with vitamin B-12 deficiency being the strongest.

CONCLUSIONS

Plasma tHcy concentration and hyperhomocysteinemia were significantly higher in this population than in previously studied populations. Vitamin B-12 and folate supplementation, concomitant lifestyle changes such as smoking cessation, and lipid-lowering treatments may help to decrease plasma tHcy concentrations and reduce the CVD risk in this population.

http://www.ncbi.nlm.nih.gov/pubmed/27273348

Zhongguo Dang Dai Er Ke Za Zhi • February 2016

Research advances in the role of vitamin D in autism spectrum disorders

Author information

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Abstract

"The etiology and pathogenic mechanism of autism spectrum disorders (ASD) are still unclear. The relationship between vitamin D and ASD has drawn attention in recent years due to common vitamin D deficiency in children with ASD. This article reviews the peripheral blood levels of vitamin D in children with ASD, the possible reasons for hypovitamin D and its possible roles in the etiology of ASD and the efficacy of vitamin D supplementation in ASD."

Full text with 76 references

http://www.cjcp.org/EN/abstract/abstract13857.shtml

“Undiagnosed metabolic B12 deficiency may be an important missed opportunity for prevention of dementia and stroke; in patients with metabolic B12 deficiency ...”

Nutrition Research • February 2016

Metabolic vitamin B12 deficiency: a missed opportunity to prevent dementia and stroke

Author information

By J.D. Spence

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Abstract

The purpose of this narrative review is to highlight insights into the importance and frequency of metabolic vitamin B12 (B12) deficiency, reasons why it is commonly missed, and reasons for the widespread but mistaken belief that treatment of B12 deficiency does not prevent stroke or improve cognitive function. Metabolic B12 deficiency is common, being present in 10%-40% of the population; is frequently missed; is easily treated; and contributes importantly to cognitive decline and stroke in older people. Measuring serum B12 alone is not sufficient for diagnosis; it is necessary to measure holotranscobalamin or functional markers of B12 adequacy such as methylmalonic acid or plasma total homocysteine. B-vitamin therapy with cyanocobalamin reduces the risk of stroke in patients with normal renal function but is harmful (perhaps because of thiocyanate accumulation from cyanide in cyanocobalamin) in patients with renal impairment. Methylcobalamin may be preferable in renal impairment. B12 therapy slowed gray matter atrophy and cognitive decline in the Homocysteine and B Vitamins in Cognitive Impairment Trial. Undiagnosed metabolic B12 deficiency may be an important missed opportunity for prevention of dementia and stroke; in patients with metabolic B12 deficiency, it would be prudent to offer inexpensive and nontoxic supplements of oral B12, preferably methylcobalamin or hydroxycobalamin. Future research is needed to distinguish the effects of thiocyanate from cyanocobalamin on hydrogen sulfide, and effects of treatment with methylcobalamin on cognitive function and stroke, particularly in patients with renal failure.

http://www.ncbi.nlm.nih.gov/pubmed/26597770

BMJ Case Reports • February 2016

Vitamin D deficiency mimicking chronic tension-type headache in children

Author information

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Abstract

"Headache, musculoskeletal pain and vitamin D deficiency, with possible inter-relationship, are common in the general population. We report cases of three premenarchal girls presenting with chronic tension-type headache and generalised body pain. The patients did not show any response to conventional therapy for tension headache. Investigations showed a severe vitamin D deficiency and biochemical osteomalacia in all three patients. The headaches and musculoskeletal pain responded markedly to vitamin D therapy. We suggest that musculoskeletal pain and headache together in a patient may be part of a single symptom complex, with vitamin D deficiency being the possible cause."

http://www.ncbi.nlm.nih.gov/pubmed/26838301

“Low vitamin D levels were common among obese adolescents living in Sweden and were strongly associated with age and associated with a higher risk of impaired fasting glycaemia.”

Acta Paediatrica • February 2016

Vitamin D deficiency is associated with pre-diabetes in obese Swedish children

Author information

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Abstract

AIM

Low vitamin D levels have been associated with obesity and living in areas that lack sunshine, such as northern Europe. The aim of this study was to investigate the vitamin D status of a group of obese children in Sweden and to investigate the associations between vitamin D status and markers of glucose metabolism and metabolic risk markers.

METHODS

This was a prospective cross-sectional study of 202 obese children between 4.5-17.9 years of age who had been referred to the National Childhood Obesity Centre at Karolinska University Hospital, Stockholm. We examined age, gender, 25-Hydroxyvitamin D (25(OH)D), f-glucose, f-insulin and metabolic risk markers. Vitamin D deficiency was defined as less than 30 25(OH)D nmol/L. Children with and without a vitamin D deficiency were compared.

RESULTS

Just over a third (33.2%) of our study population had vitamin D levels <30 nmol/L 25(OH)D. A significant interaction effect was found between age and 25(OH)D. An association was also found between low 25(OH)D levels and impaired fasting glycaemia (IFG) independent of age and season.

CONCLUSION

Low vitamin D levels were common among obese adolescents living in Sweden and were strongly associated with age and associated with a higher risk of IFG.

http://www.ncbi.nlm.nih.gov/pubmed/26871588

Clinical Calcium • March 2016

Bone disorder and nutrition

Author information

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Abstract

“The nutrition is important for prevention and improvement in bone disorder. Especially osteoporosis associated with nutrition. It has entered the super-aged society in 2007, a further increase in osteoporosis patients are concerned in Japan. Many studies have shown that associated with calcium, vitamin D, vitamin K intake and bone density and fracture. Relationship of osteoporosis and nutrition, despite the general awareness is high, calcium intake is not at all reached the achievement to recommend dietary allowance. In addition, vitamin D deficiency rickets in children, which has been considered in the past of the disorder, there is an increasing trend from such exposure shortage to the infancy of sunlight, vitamin D deficiency in pregnant women, the recommended breastfeeding. Improvement of lifestyle and diet from young age is important for bone disorder prevention.”

http://www.ncbi.nlm.nih.gov/pubmed/26923974

“Vitamin D insufficiency prevails among children ...”

Zhongguo Dang Dai Er Ke Za Zhi • March 2016

Vitamin D level in children with bloodstream infection

Author information

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Abstract

OBJECTIVE
To investigate the difference in serum 25(OH)D level between children with bloodstream infection and healthy children.

METHODS
A case-control study was conducted among 60 children with bloodstream infection who were hospitalized between January 2010 and December 2013 and had positive results of two blood cultures. Meanwhile, 60 aged-matched healthy children who underwent physical examination during the same period of time were enrolled as the healthy control group. Chemiluminescence was applied to measure the serum 25(OH)D level, and the constituent ratios of children with different serum 25(OH)D levels were compared between the two groups.

RESULTS
The bloodstream infection group had a significantly lower serum 25(OH)D level than the healthy control group ($P<0.01$). Compared with the healthy control group, the bloodstream group had significantly lower constituent ratios of children with normal Vitamin D level (8% vs 35%) or vitamin D insufficiency (22% vs 43%) ($P<0.05$). Compared with the healthy control group, the bloodstream group had significantly higher constituent ratios of children with vitamin D deficiency (42% vs 13%) or severely vitamin D deficiency (28% vs 8%) ($P<0.01$).

CONCLUSIONS
Vitamin D insufficiency prevails among children, and children with bloodstream infection have a significantly lower serum 25(OH)D level than healthy children.

http://www.ncbi.nlm.nih.gov/pubmed/26975817

“Undernutrition as well as low levels of vitamin B12 and folic acid are common problems among older adults. However, recommended routine nutritional status assessment tools may result in inadequate vitamin serum levels to go unnoticed.”

European Journal Of Clinical Nutrition • March 2016

Low serum levels of vitamin B12 in older adults with normal nutritional status by mini nutritional assessment

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Abstract

Undernutrition as well as low levels of vitamin B12 and folic acid are common problems among older adults. However, recommended routine nutritional status assessment tools may result in inadequate vitamin serum levels to go unnoticed. Therefore, the aim of this study is to evaluate the inadequacy of serum levels of vitamin B12 and folic acid within Mini Nutritional Assessment (MNA) classification categories among older adults. A cross-sectional study was conducted with 97 older adults residing in care homes in Portugal. Undernutrition was identified through the MNA, and serum levels of vitamin B12 and folic acid were measured using chemiluminescence. Cognitive function, depressive symptoms and functional characteristics were also assessed using the Abbreviated Mental Test Score, the Epidemiologic Studies Depression Scale and the Barthel Index, respectively. The mean age of older adults was 82.2 (6.3) years; 3.1% were undernourished and 26.8% were at undernutrition risk. In the MNA normal nutritional status group, 11.8% presented vitamin B12 deficiency (<200 pg/ml), 32.4% had low serum levels (200-400 pg/ml) and 4.4% had folic acid deficiency (<3 ng/ml). A high proportion of older adults with low serum levels of vitamin B12 presenting normal nutritional status by MNA was identified. This finding emphasizes the need to evaluate serum vitamin B12 levels, independently of the MNA results.

http://www.ncbi.nlm.nih.gov/pubmed/27004491

Therapeutics And Clinical Risk Management • March 2016

Allergic diseases among children: nutritional prevention and intervention

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Abstract

Allergic diseases comprise a genetically heterogeneous group of chronic, immunomediated diseases. It has been clearly reported that the prevalence of these diseases has been on the rise for the last few decades, but at different rates, in various areas of the world. This paper discusses the epidemiology of allergic diseases among children and their negative impact on affected patients, their families, and societies. These effects include the adverse effects on quality of life and economic costs. Medical interest has shifted from tertiary or secondary prevention to primary prevention of these chronic diseases among high-risk infants in early life. Being simple, practical, and cost-effective are mandatory features for any candidate methods delivering these strategies. Dietary therapy fits this model well, as it is simple, practical, and cost-effective, and involves diverse methods. The highest priority strategy is feeding these infants breast milk. For those who are not breast-fed, there should be a strategy to maintain beneficial gut flora that positively influences intestinal immunity. We review the current use of probiotics, prebiotics, and synbiotics, and safety and adverse effects. Other dietary modalities of possible potential in achieving this primary prevention, such as a Mediterranean diet, use of milk formula with modified (hydrolyzed) proteins, and the role of micronutrients, are also explored. Breast-feeding is effective in reducing the risk of asthma, allergic rhinitis, and atopic eczema among children. In addition, breast milk constitutes a major source of support for gut microbe colonization, due to its bifidobacteria and galactooligosaccharide content. The literature lacks consensus in recommending the addition of probiotics to foods for prevention and treatment of allergic diseases, while prebiotics may prove to be effective in reducing atopy in healthy children. There is insufficient evidence to support soy formulas or amino acid formulas for prevention of allergic disease. A healthy diet, such as the Mediterranean diet, may have a protective effect on the development of asthma and atopy in children. In children with asthma and allergic diseases, vitamin D deficiency correlates strongly with asthma, allergic rhinitis, and wheezing.

Full text, photos, graphs, charts and 154 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4788360/

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In children with asthma and allergic diseases,
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with asthma, allergic rhinitis, and wheezing.”

Journal Of Steroid Biochemistry And Molecular Biology • March 2016

Prevalence of Vitamin D deficiency in the North-West region of Russia: A cross-sectional study

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Abstract

“Russia is a country with geographic and economic preconditions for development of vitamin D deficiency. We analyzed serum 25(OH)D level in residents from North-West region (59-61° North latitude) of Russia to study the prevalence of vitamin D insufficiency and deficiency and its associations with gender, age, obesity and diet. The study population included 1664 residents (1544 adults 18-75 y.o. and 120 children/adolescents of 3-17 y.o.). Serum 25(OH)D was determined in 1226 participants by electrochemiluminescence immunoassay. We used a questionnaire to check the frequency of dairy and fish products intake as well as the use of vitamin supplements. The serum 25(OH)D level was 9.8-147.5nmol/L, mean level in adults population was 54.8±0.7nMol/L, in children/adolescents-46.8±1.6 nmol/L. We revealed that 16.8% of the study population had a 25(OH)D level more than 75nMol/L, 37.5% had insufficiency and 45.7% had vitamin D deficiency. Serum 25(OH)D level in women was lower than in men (53.9±0.8 and 67.2±2.2nmol/L; $p<0.01$). We did not find association between vitamin D status and age. Patients with normal BMI had higher 25(OH)D level than those with overweight and obesity (52.5±2.8 and 44.8±2.0 nmol/L, $p<0.05$). Negative correlations between 25(OH)D and BMI ($r=-0.17$, $p=0.03$) and WC ($r=-0.15$, $p=0.02$) were found. Questionnaire analyses showed that regular fish intake (minimum once per week) was associated with higher 25(OH)D level, while dairy products and vitamin supplements intake did not seem to have any effect on vitamin D status. This study showed high prevalence of vitamin D insufficiency and deficiency in adults and adolescent population from North-West region of Russia, and an association of low serum 25(OH)D level with female gender, obesity and low fish products diet.”

http://www.ncbi.nlm.nih.gov/pubmed/27013017

“Our study demonstrated a high frequency of vitamin D deficiency among Iranian children, particularly the obese ones. Moreover, low therapeutic response in the obese group is witnessed.”

Journal Of Tropical Pediatrics • March 2016

Assessment of Vitamin D Status and Response to Vitamin D3 in Obese and Non-Obese Iranian Children

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Abstract

BACKGROUND

Obesity seems to be a critical issue nowadays because of its high prevalence and its adverse effects on health. There is some evidence indicating the relationship between obesity and lower serum 25-hydroxyvitamin D [25(OH)D] concentration. The aim of the present study was to examine serum 25(OH)D status of obese and non-obese Iranian children and compare their therapeutic response with identical oral vitamin D3 treatment.

METHODS

In a non-randomized clinical trial, serum 25(OH)D level of 45 obese and 45 non-obese Iranian children aged 2-14 years was measured. Those with serum 25(OH)D status <30 ng/ml (73 cases) were treated with one pearl of vitamin D3 (50 000 International Units) once a week for 6 weeks. Serum vitamin D was measured once more 2 weeks after treatment.

RESULTS

The frequency of hypovitaminosis D was 43/45 (95.6%) in obese and 30/45 (66.7%) in non-obese children at baseline ($p < 0.001$). After treatment of 73 cases (43 obese, 30 non-obese), the above percentages were decreased to 24/43 (55.8%) and 1/30 (3.3%), respectively ($p < 0.001$).

CONCLUSION

Our study demonstrated a high frequency of vitamin D deficiency among Iranian children, particularly the obese ones. Moreover, low therapeutic response in the obese group is witnessed.

http://www.ncbi.nlm.nih.gov/pubmed/26995012

Annals Of Pediatrics (Barcelona) • March 2016

Hypovitaminosis D and associated factors in 4-year old children in northern Spain

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Abstract

INTRODUCTION

Vitamin D is an essential prohormone in calcium and phosphorus homeostasis. Recent studies show a high frequency of insufficiency/deficiency of vitamin D in the general population worldwide. Our objective was to estimate the prevalence of circulating vitamin D [25(OH)D3] deficiency and insufficiency in children and examine the associated factors.

MATERIAL AND METHODS

A total of 283 children, participants in the cohort INMA-Asturias, were studied. The 25(OH)D3 concentrations were quantified by high performance liquid chromatography. The prevalence of deficiency [25(OH)D3<20 ng/ml] and insufficiency [20-29.9 ng/ml] of vitamin D was estimated. Distribution of 25(OH)D3 for month of extraction of specimen, ingestion, and other factors were analysed.

RESULTS

The mean 25(OH)D3 was 20.1 ng/ml (range 2.7-49.8), with 8.8% ≥ 30 ng/ml, 38.5% from 20-20.9 ng/ml, and 52.7%<20 ng/ml. Seasonal variation was found, with lower values in winter. There was no relationship between plasma levels and intake of vitamin D (median 2.7µg/day, range 0.81-12.62), time outdoors (mean 3hours, range: 0:21-6:55), or BMI or gender, but there was one found with the mother's levels during gestation.

CONCLUSIONS

There is a high prevalence of vitamin D deficiency/insufficiency in children at 4 years. Solar exposure might not be enough in our region. Healthy children should be encouraged to follow adequate outdoor activities with associated sun exposure. Due the deficit of intake in childhood, recommendations are needed about a varied diet with vitamin D-containing foods in this age group, especially during the winter, and assessing the need of vitamin D supplementation in children at risk.

http://www.ncbi.nlm.nih.gov/pubmed/26988234

"There is a high prevalence of vitamin D deficiency/insufficiency in children at 4 years.

Solar exposure might not be enough in our region. Healthy children should be encouraged to follow adequate outdoor activities with associated sun exposure.

Due [to] the deficit of intake in childhood, recommendations are needed about a varied diet with vitamin D-containing foods in this age group, especially during the winter, and assessing the need of vitamin D supplementation in children at risk."

“We present a challenging diagnostic workup and management of a 42-year-old man who presentedwith anemia, thrombocytopenia, and schistocytes on peripheral smear, all pointing to microangiopathic hemolytic anemia. Vitamin B12 replacement led to normalization of the elevated levels of homocysteine, the disappearance of schistocytes on the peripheral smear, and resolution of the microangiopathic hemolysis, thereby confirming the diagnosis [B12 deficiency].”

International Journal Of Critical Illness And Injury Science • April 2016

When the picture is fragmented: Vitamin B12 deficiency masquerading as thrombotic thrombocytopenic purpura

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Abstract

Thrombotic thrombocytopenic purpura (TTP) has high mortality and necessitates prompt recognition of microangiopathic hemolytic anemia (MAHA) and initiation of plasmapheresis. We present a challenging diagnostic workup and management of a 42-year-old man who presented with anemia, thrombocytopenia, and schistocytes on peripheral smear, all pointing to MAHA. Plasmapheresis and steroid therapy were promptly initiated, but hemolysis continued. Further workup showed megaloblastic anemia, severe Vitamin B12 deficiency, high iron saturation, and absent reticulocytosis, none of which could be explained by TTP. Severe Vitamin B12 deficiency can lead to hemolytic anemia from the destruction of red cells in the marrow that have failed the process of maturation. However, this should not cause thrombotic microangiopathy. Previous reports of B12 deficiency presenting with MAHA and a TTP-like manifestation have identified acute hyperhomocysteinemia as a missing link between B12 deficiency and MAHA, so this possibility was further explored. Our patient similarly had significantly elevated serum homocysteine levels, confirming this suspicion of Vitamin B12 deficiency. Vitamin B12 replacement led to normalization of the elevated levels of homocysteine, the disappearance of schistocytes on the peripheral smear, and resolution of the microangiopathic hemolysis, thereby confirming the diagnosis. It is pertinent that intensivists not only know the importance of early recognition and treatment of TTP but are also familiar with rare conditions that can present in a similar fashion.

http://www.ncbi.nlm.nih.gov/pubmed/27308258

Brain And Nerve • April 2016

Treatable Dementia due to Vitamin B12 and Folate Deficiency

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Abstract

“Vitamin deficiency is one of the major causes of treatable dementia. Specifically, patients suffering from dementia frequently display low serum levels of vitamin B(12). There is a close metabolic interaction between folate and vitamin B(12). Folate deficiency causes various neuropsychiatric symptoms, which resemble those observed in vitamin B(12) deficiency. This review summarizes, the basic pathophysiology of vitamin B(12) and folate deficiency, its clinical diagnosis, associated neuropsychiatric symptoms such as subacute combined degeneration and dementia, and epidemiological studies of cognitive decline and brain atrophy.”

http://www.ncbi.nlm.nih.gov/pubmed/27056859

Pediatric Blood And Cancer • April 2016

Vitamin B12 Deficiency in Infancy: The Case for Screening

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Abstract

"The classic principles put forth by Wilson and Jungner are often applied to determine the suitability of a condition for universal newborn screening. The three cases described here portray the harmful effects of vitamin B12 deficiency in infancy. The challenges and opportunities of early recognition and treatment are highlighted. Screening newborns would allow early detection and prevention of severe neurological damage in vitamin B12 -deficient infants and enable diagnosis of unrecognized maternal pernicious anemia in asymptomatic mothers. However, lack of standardized methodology and screening cutoffs present challenges to the use of current tandem mass spectrometry technologies for screening."

http://www.ncbi.nlm.nih.gov/pubmed/26806811

“In this study, we showed for the first time that olfactory dysfunction may be present in patients with vitamin B12 deficiency. Apart from a negative correlation of age with odor identification score, none of the other parameters studied showed correlations with olfactory dysfunction.”

International Forum On Allergy & Rhinology • April 2016

Effect of vitamin B12 deficiency on olfactory function

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Abstract

BACKGROUND

Vitamin B12 plays a major role in the maintenance of central and peripheral nervous systems. Vitamin B12 deficiency may affect the spinal cord, brain, optic nerve, and peripheral nerve functions; however, the effect of vitamin B12 deficiency on olfactory function has not been studied, so our study aimed to investigate that.

METHODS

Thirty-nine patients with low vitamin B12 levels and 34 controls were included in the study. All participants had detailed otorhinolaryngological examinations and laboratory tests. The Sniffin' Stick test was used for analysis of olfactory function. The 2 groups were compared for smell test results. Correlations of smell test results with demographic and laboratory data were investigated in the vitamin B12-deficient group.

RESULTS

The threshold discrimination identification scores were (mean ± standard deviation) 28.04 ± 5.58 and 35.10 ± 2.84 in the vitamin B12-deficient and control groups, respectively ($p < 0.001$). In the vitamin B12-deficient group, hyposmia and anosmia were evident in 56.4% and 5.1% of the patients, respectively, but no subjects in the control group had olfactory dysfunction ($p < 0.001$). Correlation analysis showed that age and odor identification score showed a negative correlation ($p < 0.001$); however, there was a positive correlation between threshold, discrimination and identification (TDI) score and vitamin B12 levels.

CONCLUSION

In this study, we showed for the first time that olfactory dysfunction may be present in patients with vitamin B12 deficiency. Apart from a negative correlation of age with odor identification score, none of the other parameters studied showed correlations with olfactory dysfunction.

http://www.ncbi.nlm.nih.gov/pubmed/27119316

“Our meta-analysis found that lower maternal vitamin D during pregnancy was associated with an increased risk of childhood eczema ...”

Pediatric Allergy And Immunology • May 2016

Maternal vitamin D status and childhood asthma, wheeze and eczema: a systematic review and meta-analysis

Author information

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Abstract

BACKGROUND

Maternal vitamin D status has been reported to be associated with childhood allergic diseases. However, this association remains to be fully elucidated.

METHODS

A systematic review and meta-analysis was conducted using prospective cohort studies that examined the association between maternal vitamin D status and childhood allergic diseases including wheeze, eczema and asthma. We searched electronic databases of PubMed, EMBASE, the Cochrane library, the Wanfang (Chinese) database, the VIP (Chinese) database, and Chinese National Knowledge Infrastructure (CNKI) up to August 2014. Odds ratios and 95% confidence intervals (CIs) from individual studies were synthesized using a fixed effects model.

RESULTS

Four studies on the association between maternal vitamin D status and childhood asthma (3666 mother-child pairs), four studies on the association between maternal vitamin D status and childhood wheeze (2225 mother-child pairs) and three papers on the association between maternal vitamin D status and childhood eczema (2172 mother-child pairs) met our inclusion criteria. Maternal vitamin D status during pregnancy was associated with childhood eczema (pooled OR=0.904, 95% CI=0.831-0.983). However, the meta-analysis showed no statistical association between maternal vitamin D status and childhood asthma (pooled OR=0.981, 95% CI=0.944-1.019) or childhood wheeze (pooled OR=0.995, 95% CI=0.982-1.009).

CONCLUSIONS

Our meta-analysis found that lower maternal vitamin D during pregnancy was associated with an increased risk of childhood eczema but was not associated with childhood asthma or wheeze. The role of maternal vitamin D as an important protective factor for the development of childhood eczema remains to be elucidated.

http://www.ncbi.nlm.nih.gov/pubmed/27145360

“In this study, a shorter injection regime is probably not sufficient to treat a vitamin B12 deficiency. An injection regime with 6 injections recovered all vitamin B12 deficiencies biochemically.”

Obesity Surgery • May 2016

Comparison Between Different Intramuscular Vitamin B12 Supplementation Regimes: a Retrospective Matched Cohort Study

Author information

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Abstract

BACKGROUND

The incidence of vitamin B12 deficiency after bariatric surgery can range from 26 to 70 %. There is no consensus on optimal vitamin B12 supplementation in postbariatric patients. The objective of this study was to compare three different regimes.

METHODS

In this retrospective matched cohort study, we included 63 patients with methylmalonic acid (MMA) levels ≥300 nmol/L. Group A (n=21) received 6 intramuscular (im) vitamin B12 injections including a loading dose, group B (n=21) received 3 im vitamin B12 injections without loading dose and group C (n=21) received no im vitamin B12 injections.

RESULTS

The total post-bariatric patient population consisted of 14 males (22.2 %) and 49 women (77.8 %) with a mean current body mass index of 30.6±8.0 kg/m2. There was no significant difference in vitamin B12 and MMA levels between 3 groups at baseline. There was a significant difference in follow-up vitamin B12 levels of group A compared to group B ($p=0.02$) and group A compared to group C ($p=0.03$). In the follow-up results, there is also a significant decrease in MMA levels of group A compared to group B ($p=0.02$), group A compared to group C ($p<0.001$), and group B compared to group C ($p<0.01$).

CONCLUSIONS

In this study, a shorter injection regime is probably not sufficient to treat a vitamin B12 deficiency. An injection regime with 6 injections recovered all vitamin B12 deficiencies biochemically. MMA levels cannot recover spontaneously over time without additional im injection regime.

http://www.ncbi.nlm.nih.gov/pubmed/27146501

“Our findings suggest that Thiamine deficiency is highly prevalent among inpatients with cancer, even among normal and overweight individuals, in the absence of other vitamin deficiencies, and while receiving multivitamin supplements. Evaluation of Thiamine deficiency was most commonly not initiated by oncologists. Failure to treat and treatment delay were common.”

Psychooncology • May 2016

High rate of thiamine deficiency among inpatients with cancer referred for psychiatric consultation: results of a single site prevalence study

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Abstract

OBJECTIVE

Thiamine deficiency (TD) is increasingly recognized in medically ill patients. The prevalence of TD among cancer patients is unknown. This study aims to characterize the prevalence of TD among inpatients with cancer.

METHODS

Retrospective chart review of patients admitted to a large cancer center who were referred for psychiatric consultation and whose serum thiamine concentration was measured. Patients with alcohol use were excluded.

RESULTS

Among 217 patients with various cancer types, TD was found in 55.3%. Risk factors included fluorouracil-based chemotherapy, significant weight loss, and undergoing active cancer treatment. Almost all patients were normal weight, overweight, or obese, and few had concomitant vitamin B12 or folate deficiency. A total of 17.5% were receiving multivitamin supplementation. Nearly half (49.8%) did not receive empiric treatment with thiamine and among those who did, treatment delay occurred in the majority of cases (59.6%). Measurement of serum thiamine concentration preceded psychiatric consultation in only 10.6% of cases.

CONCLUSIONS

Our findings suggest that TD is highly prevalent among inpatients with cancer, even among normal and overweight individuals, in the absence of other vitamin deficiencies, and while receiving multivitamin supplements. Several potential risk factors were identified, including active cancer treatment. Evaluation of TD was most commonly not initiated by oncologists. Failure to treat and treatment delay were common. Given these findings, oncologists must be vigilant about detecting TD among inpatients with cancer.

http://www.ncbi.nlm.nih.gov/pubmed/27228202

“Insufficient maternal 25(OH)D during pregnancy may increase the risk of MS in offspring.”

JAMA Neurology • May 2016

Vitamin D Status During Pregnancy and Risk of Multiple Sclerosis in Offspring of Women in the Finnish Maternity Cohort

Author information

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Abstract

IMPORTANCE

Vitamin D has been associated with a decreased risk of multiple sclerosis (MS) in adulthood; however, some, but not all, previous studies have suggested that in utero vitamin D exposure may be a risk factor for MS later in life.

OBJECTIVE

To examine whether serum 25-hydroxyvitamin D (25[OH]D) levels in early pregnancy are associated with risk of MS in offspring.

DESIGN, SETTING, AND PARTICIPANTS

Prospective, nested case-control study in the Finnish Maternity Cohort conducted in May 2011. We identified 193 individuals with a diagnosis of MS before December 31, 2009, whose mothers are in the Finnish Maternity Cohort and had an available serum sample from the pregnancy with the affected child. We matched 176 cases with 326 controls on region of birth in Finland, date of maternal serum sample collection, date of mother’s birth, and date of child’s birth.

MAIN OUTCOMES AND MEASURES

Maternal serum 25(OH)D levels were measured using a chemiluminescence assay. The risk of MS among offspring and association with maternal 25(OH)D levels were the main outcomes. Conditional logistic regression was used and further adjusted for sex of the child, gestational age at the time of sample collection, and season of sample collection to estimate the relative risks and 95% CIs.

RESULTS

Of the 193 cases in the study, 163 were female. Of the 331 controls in the study, 218 were female. Seventy percent of serum samples were collected during the first trimester of pregnancy. The mean (SD) maternal vitamin D levels were in the insufficient vitamin D range, but higher in maternal control than case samples (15.02 [6.41] ng/mL vs 13.86 [5.49] ng/mL [to convert to nanomoles per liter, multiply by 2.496]). Maternal vitamin D deficiency (25[OH]D levels <12.02 ng/mL) during early pregnancy was associated with a nearly 2-fold increased risk of MS in the offspring (relative risk, 1.90; 95% CI, 1.20-3.01; P=.006) compared with women who did not have deficient 25(OH)D levels. There was no statistically significant association between the risk of MS and increasing serum 25(OH)D levels (P=.12).

CONCLUSIONS AND RELEVANCE

Insufficient maternal 25(OH)D during pregnancy may increase the risk of MS in offspring.

http://www.ncbi.nlm.nih.gov/pubmed/26953778

Springerplus • May 2016

Holotranscobalamin (HoloTC, Active-B12) and Herbert's model for the development of vitamin B12 deficiency: a review and alternative hypothesis

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Abstract

"The concentration of total vitamin B12 in serum is not a sufficiently sensitive or specific indicator for the reliable diagnosis of vitamin B12 deficiency. Victor Herbert proposed a model for the staged development of vitamin B12 deficiency, in which holotranscobalamin (HoloTC) is the first indicator of deficiency. Based on this model, a commercial immunoassay has been controversially promoted as a replacement for the total vitamin B12 test. HoloTC is cobalamin (vitamin B12) attached to the transport protein transcobalamin, in the serum, for delivery to cells for metabolism. Although there have been many published reports supporting the claims for HoloTC, the results of some studies were inconsistent with the claim of HoloTC as the most sensitive marker of vitamin B12 deficiency. This review examines the evidence for and against the use of HoloTC, and concludes that the HoloTC immunoassay cannot be used to measure vitamin B12 status any more reliably than total vitamin B12, or to predict the onset of a metabolic deficiency, because it is based on an erroneous hypothesis and a flawed model for the staged development of vitamin B12 deficiency. The author proposes an alternative model for the development of vitamin B12 deficiency."

Full text, graphs, charts and 110 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4899389/

“Vitamin D deficiency [is] associated with pregnancy loss in the first trimester of pregnancy. Decreased serum vitamin D levels among childbearing aged women with the failed clinical pregnancies history may predispose to increased risk for pregnancy loss.”

European Journal Of Clinical Nutrition • May 2016

Decreased serum vitamin D levels in early spontaneous pregnancy loss

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Abstract

BACKGROUND/OBJECTIVES

Effects of vitamin D deficiency in pregnancy have been associated with some adverse pregnancy outcomes. The objective of this study was to analyze the relationship between vitamin D deficiency in childbearing aged women and pregnancy loss (PL) in the first trimester.

SUBJECTS/METHODS

This is a cross-sectional study. Plasma was collected from 60 nulliparous women with singleton at 7-9 weeks of gestation (30 with viable gestation and 30 with PL) and 60 non-gravid childbearing aged women (30 with a successful pregnancy history, and 30 with one or more spontaneous first-trimester PL history). Quantitation of serum 25-hydroxyvitamin D (25(OH)D) and 25-hydroxyvitamin D-1 alpha hydroxylase (CYP27B1) was assayed.

RESULTS

By pregnancy/non-gravid, normal pregnant women had higher 25(OH)D (49.32 µg/l) and CYP27B1 (82.00 pg/ml) than PL women (34.49 µg/l and 37.87 pg/ml, both $P<0.01$); the non-gravid women with a successful pregnancy history also had higher 25(OH)D (39.56 µg/l) and CYP27B1 (39.04 pg/ml) than women with PL history (12.30 µg/l and 12.35 pg/ml, both $P<0.01$). The 96.7% of non-gravid women with PL history and 43.3% of PL women had serum 25(OH)D concentrations below 30 µg/l. There was a strong association between low vitamin D levels and PL (odds ratio 1.71; 95% confidence interval: 1.2-2.4, $P<0.001$). The regression analyses showed that PL was significantly inversely correlated with 25(OH)D ($P<0.01$) and CYP27B1 levels ($P<0.01$).

CONCLUSIONS

Vitamin D deficiency associated with PL in the first trimester of pregnancy. Decreased serum vitamin D levels among childbearing aged women with the failed clinical pregnancies history may predispose to increased risk for PL.

http://www.ncbi.nlm.nih.gov/pubmed/27222154

Tropical Doctor • May 2016

Vitamin D deficiency and lower respiratory tract infections in children: a systematic review and meta-analysis of observational studies

Author information

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Abstract

“Studies related to vitamin D deficiency and lower respiratory tract infections (LRTI) in children have inconsistent findings. The objective of this systematic review was to assess the prevalence of vitamin D deficiency in children with LRTI, and to evaluate the correlation between vitamin D levels and the incidence and severity of LRTI. A total of 12 studies enrolling 2279 participants were included in our analysis. Children with LRTI were found to have significantly lower mean vitamin D levels as compared to controls. There was likewise a correlation between vitamin D levels and incidence and severity of LRTI. Large randomised controlled trials are needed to evaluate effect of vitamin D supplementation for LRTI.”

http://www.ncbi.nlm.nih.gov/pubmed/27178217

BMJ Case Reports • May 2016

Nitrous oxide misuse and vitamin B12 deficiency

Author information

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Abstract

“A 36-year-old man presented to hospital with a 5-week history of ascending limb paraesthesiae and balance difficulties. He had no medical or travel history of note, but admitted habitual nitrous oxide (N2O) inhalation. Neurological examination revealed a sensory ataxia with pseudoathetosis in the upper limbs and reduced vibration sensation to the hips bilaterally. Significant investigation results included a low serum vitamin B12 concentration, mild macrocytosis and raised serum homocysteine concentration. T2 MRI of the spinal cord demonstrated increased signal extending from C1 to T11 in keeping with a longitudinal myelitis. The patient was diagnosed with a myeloneuropathy secondary to vitamin B12 deficiency, resulting from heavy N2O inhalation. He was treated with intramuscular vitamin B12 injections and received regular physiotherapy. At discharge, he was able to mobilise short distances with the aid of a zimmer frame, and was independently mobile 8 weeks later.”

http://www.ncbi.nlm.nih.gov/pubmed/27247211

“No single laboratory marker is suitable for the assessment of B12 status in all patients. Sequential assay selection algorithms or the combination of multiple markers into a single diagnostic indicator are both approaches that can be used to mitigate inherent limitations of each marker when used independently.”

Journal Of Clinical Pathology • May 2016

Laboratory assessment of vitamin B12 status

Author information

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Abstract

The detection and correction of vitamin B12 (B12) deficiency prevents megaloblastic anaemia and potentially irreversible neuropathy and neuropsychiatric changes. B12 status is commonly estimated using the abundance of the vitamin in serum, with ~148 pmol/L (200 ng/L) typically set as the threshold for diagnosing deficiency. Serum B12 assays measure the sum of haptocorrin-bound and transcobalamin-bound (known as holotranscobalamin) B12 It is only holotranscobalamin that is taken up by cells to meet metabolic demand. Although receiver operator characteristic curves show holotranscobalamin measurement to be a moderately more reliable marker of B12 status than serum B12, both assays have an indeterminate range. Biochemical evidence of metabolic abnormalities consistent with B12 insufficiency is frequently detected despite an apparently sufficient abundance of the vitamin. Laboratory B12 status markers that reflect cellular utilisation rather than abundance are available. Two forms of B12 act as coenzymes for two different reactions. Methionine synthase requires methylcobalamin for the remethylation of methionine from homocysteine. A homocysteine concentration >20 µmol/L may suggest B12 deficiency in folate-replete patients. In the second B12-dependent reaction, methylmalonyl-CoA mutase uses adenosylcobalamin to convert methylmalonyl-CoA to succinyl-CoA. In B12 deficiency excess methylmalonyl-CoA is hydrolysed to methylmalonic acid. A serum concentration >280 nmol/L may suggest suboptimal status in young patients with normal renal function. No single laboratory marker is suitable for the assessment of B12 status in all patients. Sequential assay selection algorithms or the combination of multiple markers into a single diagnostic indicator are both approaches that can be used to mitigate inherent limitations of each marker when used independently.

http://www.ncbi.nlm.nih.gov/pubmed/27169753

“The most effective dose of Micronutrients has rarely been tested systematically. Micronutrient interventions alone are not very effective for improving the growth and development of young children. Newer methods for the analysis of Micronutrients in breast milk are revealing low concentrations in many populations, so more information is needed on the effects of different interventions on milk nutrient content. We need to improve biomarkers of Micronutrient status and should measure multiple biological responses to Micronutrient interventions using modern nutritional science methods, including metabolomics, proteomics and epigenetics; these will reveal effects of Micronutrients that are not yet fully appreciated.”

World Review Of Nutrition And Dietetics • May 2016

Current Information Gaps in Micronutrient Research, Programs and Policy: How Can We Fill Them?

Author information

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Abstract

Micronutrient (MN) interventions have a very positive effect on public health and have been a major focus of nutrition research and policy for over 3 decades. Most MN policies are established by the World Health Organization based on available evidence from well-designed trials. These include recommendations on iron + folic acid supplements for pregnancy, high-dose vitamin A supplementation for children <5 years, multiple MN supplementation in young children, food fortification, and universal salt iodization. However, important gaps remain in the evidence base, some periods of the life span have been paid insufficient attention, and some MN policies are incomplete or inconsistent. Examples include the pending decision about whether to recommend multiple MN supplementation in pregnancy or preconception, a lack of information about whether supplementation of lactating women improves breast milk quality and infant development, uncertainty about when and where fortification of complementary foods or supplements is beneficial to preschoolers, and whether folic acid fortification can be harmful in population groups with a high prevalence of vitamin B12 deficiency. The most effective dose of MNs has rarely been tested systematically. MN interventions alone are not very effective for improving the growth and development of young children. Newer methods for the analysis of MNs in breast milk are revealing low concentrations in many populations, so more information is needed on the effects of different interventions on milk nutrient content. We need to improve biomarkers of MN status and should measure multiple biological responses to MN interventions using modern nutritional science methods, including metabolomics, proteomics and epigenetics; these will reveal effects of MNs that are not yet fully appreciated.

http://www.ncbi.nlm.nih.gov/pubmed/27198672

European Journal Of Clinical Nutrition • May 2016

What is the safe upper intake level of folic acid for the nervous system? Implications for folic acid fortification policies

Author information

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Abstract

"Between 1945 and 1959 it was convincingly documented that folic acid can precipitate or aggravate the neurological and haematological consequences of vitamin B12 deficiency by increasing the demand for vitamin B12. Since then there has been much misunderstanding of the issues, mainly by advocates of folic acid fortification who have been inclined to minimise or even dismiss the risks by misinterpreting the evidence as only a 'masking' of the anaemia of pernicious anaemia. Recent studies in the era of fortification are rediscovering the risks to the nervous system, especially cognitive function, of excess folate in the presence of vitamin B12 deficiency. I have reviewed the Reports of four Expert Advisory Committees in Europe and the USA, which suggest that the safe upper tolerable limit (UL) for folic acid is 1 mg in adults. These reports are unsound and there is already evidence of neurological harm from long-term exposure to doses of folic acid between 0.5 and 1 mg in the presence of vitamin B12 deficiency. There is an urgent need to review the safe UL for folic acid and to consider the addition of vitamin B12 to folic acid fortification policies."

http://www.ncbi.nlm.nih.gov/pubmed/26862004

Indian Dermatology Online Journal • May 2016

Reticulate pigmentation associated with vitamin B12 deficiency

Author information

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Full text, photos and 10 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4886604/

“Low maternal 25(OH)D concentrations are associated with proportional fetal growth restriction and with an increased risk of preterm birth and small size for gestational age at birth.”

American Journal Of Clinical Nutrition • June 2016

Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes

Miliku K1, Vinkhuyzen A2, Blanken LM3, McGrath JJ2, Eyles DW2,
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Abstract

BACKGROUND
Maternal vitamin D deficiency during pregnancy may affect fetal outcomes.
OBJECTIVE
The objective of this study was to examine whether maternal 25-hydroxyvitamin D [25(OH)D] concentrations in pregnancy affect fetal growth patterns and birth outcomes.
DESIGN
This was a population-based prospective cohort in Rotterdam, Netherlands in 7098 mothers and their offspring. We measured 25(OH)D concentrations at a median gestational age of 20.3 wk (range: 18.5-23.3 wk). Vitamin D concentrations were analyzed continuously and in quartiles. Fetal head circumference and body length and weight were estimated by repeated ultrasounds, and preterm birth (gestational age <37 wk) and small size for gestational age (less than the fifth percentile) were determined.
RESULTS
Adjusted multivariate regression analyses showed that, compared with mothers with second-trimester 25(OH)D concentrations in the highest quartile, those with 25(OH)D concentrations in the lower quartiles had offspring with third-trimester fetal growth restriction, leading to a smaller head circumference, shorter body length, and lower body weight at birth (all $P < 0.05$). Mothers who had 25(OH)D concentrations in the lowest quartile had an increased risk of preterm delivery (OR: 1.72; 95% CI: 1.14, 2.60) and children who were small for gestational age (OR: 2.07; 95% CI: 1.33, 3.22). The estimated population attributable risk of 25(OH)D concentrations <50 nmol/L for preterm birth or small size for gestational age were 17.3% and 22.6%, respectively. The observed associations were not based on extreme 25(OH)D deficiency, but presented within the common ranges.
CONCLUSIONS
Low maternal 25(OH)D concentrations are associated with proportional fetal growth restriction and with an increased risk of preterm birth and small size for gestational age at birth. Further studies are needed to investigate the causality of these associations and the potential for public health interventions.

http://www.ncbi.nlm.nih.gov/pubmed/27099250

“Evidence from high income countries shows mothers who are supplemented with folic acid in their periconceptional period and early pregnancy have significantly reduced adverse outcomes like birth defects.”

JMIR Research Protocols • June 2016

A Mixed-Method Study to Determine the Benefits of Periconceptional Folic Acid Supplementation and Effects of Folic Acid Deficiency in Mothers on Birth Outcomes

Author information

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Abstract

BACKGROUND

Evidence from high income countries shows mothers who are supplemented with folic acid in their periconceptional period and early pregnancy have significantly reduced adverse outcomes like birth defects. However, in India there is a paucity of data on association of birth defects and folic acid supplementation. We identified a few important questions to be answered using separate scientific methods and then planned to triangulate the information.

OBJECTIVE

In this paper, we describe the protocol of our study that aims to determine the association of folic acid and pregnancy outcomes like neural tube defects (NTDs) and orofacial clefts (OFCs). We decided to fill the gaps in knowledge from India to determine public health consequences of folic acid deficiency and factors influencing dietary and periconceptional consumption of folic acid.

METHODS

The proposed study will be carried out in five stages and will examine the questions related to folic acid deficiency across selected locations in South and North India. The study will be carried out over a period of 4 years through the hierarchical evidence-based approach. At first a systematic review was conducted to pool the current birth prevalence of NTDs and orofacial clefts OFCs in India. To investigate the population prevalence, we plan to use the key informant method to determine prevalence of NTDs and OFCs. To determine the normal serum estimates of folic acid, iron, and vitamin B12 among Indian women (15-35 years), we will conduct a population-based, cross-sectional study. We will further strengthen the evidence of association between OFCs and folic acid by conducting a hospital-based, case-control study across three locations of India. Lastly, using qualitative methods we will understand community and health workers perspective on factors that decide the intake of folic acid supplements.

RESULTS

This study will provide evidence on the community prevalence of birth defects and prevalence folic acid and vitamin B12 deficiency in the community. The case-control study will help understand the association of folic acid deficiency with OFCs.

CONCLUSIONS

The results from this study are intended to strengthen the evidence base in childhood disability for planning and policy initiatives.

http://www.ncbi.nlm.nih.gov/pubmed/27339656

Journal Of Pediatric Hematology And Oncology • June 2016

Profound Vitamin B12 Deficiency in a 1-Year-Old Child in Botswana: A Call to Initiate Early Empiric Therapy

Author information

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Abstract

"Vitamin B12 deficiency is a rare diagnosis in young children. We present the case of a 1-year-old Zimbabwean child with profound anemia. Further testing revealed undetectable levels of vitamin B12 and positive intrinsic factor antibodies that were drawn after the initiation of empiric treatment with parenteral vitamin B12. We report the evaluation and management of vitamin B12 deficiency in a resource-limited setting. Vitamin B12 deficiency should be considered in children presenting with unexplained cytopenias with consideration of empiric treatment with parenteral vitamin B12, as developmental and neurological complications of vitamin B12 deficiency can be devastating and permanent."

http://www.ncbi.nlm.nih.gov/pubmed/27306229

Pediatric And Developmental Pathology • June 2016

Hematogones detected by flow cytometry in a child with vitamin B12 deficiency: A case report

Author information
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Abstract

"Vitamin B12 deficiency is a known cause of megaloblastic anemia and bone marrow failure. Bone marrow biopsies are not frequently performed as part of the diagnostic workup and can demonstrate morphologic features that overlap with myelodysplastic syndrome (MDS) and acute leukemia. We describe a case of a dysplastic bone marrow with increased bone marrow hematogones detected by flow cytometry in a child with vitamin B12 deficiency. Hematogones are normal B cell precursors, and hyperplasia has been described in a variety of often reactive conditions and also disease. Hematogones are not typically seen in MDS. The presence of hematogones may help differentiate the dysplastic changes seen in vitamin B12 deficiency from MDS."

http://www.ncbi.nlm.nih.gov/pubmed/27285990

“The prevalence of vitamin B12 deficiency varies from 5.8% to 30% among patients undergoing long-term treatment with metformin.”

Sao Paulo Medical Journal • June 2016

Prevalence of vitamin B12 deficiency in type 2 diabetic patients using metformin: a cross-sectional study

Author information

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Abstract

CONTEXT AND OBJECTIVE

The prevalence of vitamin B12 deficiency varies from 5.8% to 30% among patients undergoing long-term treatment with metformin. Because of the paucity of data on Brazilian patients, this study aimed to determine the frequency of B12 deficiency and related factors among Brazilian patients with type 2 diabetes mellitus (T2DM) using metformin.

DESIGN AND SETTING

Cross-sectional study at a public university hospital.

METHODS

Patients with T2DM and a control group of non-diabetics were included. Serum B12 levels were measured and biochemical B12 deficiency was defined as serum levels < 180 pg/ml. Associations between B12 deficiency and age, duration of T2DM, duration of use and dosage of metformin, and use of proton pump inhibitors (PPIs) or histamine H2 antagonists were determined.

RESULTS

231 T2DM patients using metformin (T2DM-met) and 231 controls were included. No difference in the frequency of PPI or H2-antagonist use was seen between the groups. B12 deficiency was more frequent in the T2DM-met group (22.5% versus 7.4%) and this difference persisted after excluding PPI/H2-antagonist users (17.9% versus 5.6%). The factors that interfered with serum B12 levels were PPI/H2-antagonist use and duration of metformin use ≥ 10 years. Use of PPI/H2-antagonists was associated with B12 deficiency, with an odds ratio of 2.60 (95% confidence interval, 1.34-5.04).

CONCLUSIONS

Among T2DM patients, treatment with metformin and concomitant use of PPI/H2-antagonists are associated with a higher chance of developing B12 deficiency than among non-diabetics.

http://www.ncbi.nlm.nih.gov/pubmed/27276084

“Malnutrition continues to be a major public health problem in countries with weak infrastructures. In communities with a high prevalence of poor diet, malnourishment and infectious disease can impact vulnerable individuals such as pregnant women and children. Here, we describe a highly flexible murine model for monitoring maternal and environmental influences of vitamin B12 metabolism. We also demonstrate the potential importance of vitamin B12 in controlling susceptibility to bacterial pathogens such as C. rodentium and S Typhimurium.”

Molecular Biology • June 2016

Infection Susceptibility in Gastric Intrinsic Factor (Vitamin B12)-Defective Mice Is Subject to Maternal Influences

Author information

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Abstract

Mice harboring a mutation in the gene encoding gastric intrinsic factor (Gif), a protein essential for the absorption of vitamin B12/cobalamin (Cbl), have potential as a model to explore the role of vitamins in infection. The levels of Cbl in the blood of Gif(tm1a/tm1a) mutant mice were influenced by the maternal genotype, with offspring born to heterozygous (high Cbl, F1) mothers exhibiting a significantly higher serum Cbl level than those born to homozygous (low Cbl, F2) equivalents. Low Cbl levels correlated with susceptibility to an infectious challenge with Salmonella enterica serovar Typhimurium or Citrobacter rodentium, and this susceptibility phenotype was moderated by Cbl administration. Transcriptional and metabolic profiling revealed that Cbl deficient mice exhibited a bioenergetic shift similar to a metabolic phenomenon commonly found in cancerous cells under hypoxic conditions known as the Warburg effect, with this metabolic effect being exacerbated further by infection. Our findings demonstrate a role for Cbl in bacterial infection, with potential general relevance to dietary deficiency and infection susceptibility.

IMPORTANCE

Malnutrition continues to be a major public health problem in countries with weak infrastructures. In communities with a high prevalence of poor diet, malnourishment and infectious disease can impact vulnerable individuals such as pregnant women and children. Here, we describe a highly flexible murine model for monitoring maternal and environmental influences of vitamin B12 metabolism. We also demonstrate the potential importance of vitamin B12 in controlling susceptibility to bacterial pathogens such as C. rodentium and S Typhimurium. We postulate that this model, along with similarly vitamin deficient mice, could be used to further explore the mechanisms associated with micronutrients and susceptibility to diseases, thereby increasing our understanding of disease in the malnourished.

Full text, photos, graphs, charts and 38 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4916386/

“The frequency of vitamin D deficiency and insufficiency was higher in children with asthma, compared to the controls. Therefore, we suggest that lower levels of vitamin D are associated with poor asthma control and increased asthma severity.”

European Reviews In Medicine And Pharmacology Science • June 2016

Effects of vitamin D levels on asthma control and severity in pre-school children

Author information
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Abstract

OBJECTIVE
Prevalence of asthma and vitamin D deficiency has been increasing and leading to significant morbidities. This study aimed to compare the vitamin D levels in the pre-school children with asthma and in healthy controls and to assess the relationship between vitamin D levels and asthma clinical parameters and control.

PATIENTS AND METHODS
Vitamin D [25(OH)D3] levels were measured in 102 pre-school children, aged 1-4 years with asthma and 102 healthy controls in winter. The patients with asthma were grouped according to serum vitamin D levels as sufficient, insufficient and deficient. Asthma control was classified according to the Global Initiative for Asthma (GINA) guidelines and the Test for Respiratory and Asthma Control in Kids (TRACK) in 1-4 years-old children.

RESULTS
Serum vitamin D levels were 22.64 (9.96) ng/ml in the asthma group and 32.11 (14.74) ng/ml in the control group ($p = 0.001$). Total number of exacerbations during the previous year were significantly lower in the vitamin D sufficient group, compared to the deficient and insufficient groups ($p = 0.03$). Frequency of patients with controlled asthma was higher in the sufficient group compared to the deficient and insufficient groups ($p = 0.001$ and $p = 0.001$, respectively). There was a positive correlation between serum vitamin D levels and asthma control.

CONCLUSIONS
The frequency of vitamin D deficiency and insufficiency was higher in children with asthma, compared to the controls. Therefore, we suggest that lower levels of vitamin D are associated with poor asthma control and increased asthma severity.

Full text, PDF, graphs, charts and 42 references

http://www.europeanreview.org/wp/wp-content/uploads/26-36.pdf

“Vitamin D deficiency was associated with pulmonary function deficits among obese children, but not among normal-weight children with asthma, an association that was independent of Th1 and Th2 serum inflammatory measures. Vitamin D deficiency may be one potential mechanism underlying the obese-asthma phenotype.”

Pediatric Pulmonology • June 2016

Vitamin D and pulmonary function in obese asthmatic children

Author information

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Abstract

OBJECTIVE

Asthma-related morbidity is higher among children with vitamin D deficiency and obesity, morbidities that frequently co-exist among minority children. However, the effect of co-existent obesity and vitamin D deficiency on pulmonary function is poorly understood.

METHODS

We compared percent-predicted values of pulmonary function across vitamin D categories among 72 obese and 71 normal-weight Hispanic and African-American children with asthma recruited at an urban children’s hospital. Serum cytokines associated with Th1 and Th2 inflammation and 25-hydroxyvitamin D (25-OHD) were quantified in fasting serum. 25-OHD levels ≥30 ng/ml were categorized as sufficient, <30 and ≥20 ng/ml as insufficient, and <20 ng/ml as deficient. The role of inflammation was investigated by regression analysis.

RESULTS

Vitamin D deficiency was present in 50% of children and did not differ by obese status. Forced Expiratory Volume in the first second (84.5 ± 9.4 vs. 94.8 ± 8.4, $P < 0.001$), and Functional Residual Capacity (67.5 ± 20.1 vs. 79.3 ± 19, $P = 0.01$) were lower among vitamin D deficient obese asthmatics than their sufficient counterparts, and Total Lung Capacity was lower than their insufficient counterparts (86.9 ± 14.3 vs. 96.6 ± 10, $P = 0.01$); similar associations were not observed in normal-weight asthmatics and were not influenced by systemic inflammation. No association between Th1 and Th2 inflammatory measures, vitamin D deficiency, and pulmonary function tests was found.

CONCLUSIONS

Vitamin D deficiency was associated with pulmonary function deficits among obese children, but not among normal-weight children with asthma, an association that was independent of Th1 and Th2 serum inflammatory measures. Vitamin D deficiency may be one potential mechanism underlying the obese-asthma phenotype.

http://www.ncbi.nlm.nih.gov/pubmed/27273785

“This retrospective chart review study aimed to assess vitamin D status and identify risk factors associated with vitamin D deficiency and bone parameters in children with cancer at admission.”

Nutrition And Cancer • June 2016

The Incidence of and Factors Associated with Vitamin D Deficiency in Newly Diagnosed Children with Cancer

Author information

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Abstract

This retrospective chart review study aimed to assess vitamin D status and identify risk factors associated with vitamin D deficiency and bone parameters in children with cancer at admission. The data of 86 (50 males and 36 females) patients between April 2013 and June 2015 were analyzed. Calcium, phosphorus, alkaline phosphatase (ALP), 25(OH)D, age, gender, diagnostic category, body mass index, duration of complaints, and season of blood sampling were recorded. Median age was 7.17 years (range 0.31-17.40) in 29 hematological malignancy and 57 solid tumor patients. According to cut-off level of 20 ng/ml, 63% of children with cancer had vitamin D deficiency at diagnosis with a median 25(OH)D of 16.75 ng/ml. The mean vitamin D value of children >10 years was significantly low in comparison to that observed in younger children [11.83, 95% confidence interval (CI) = = 8.85-14.81 ng/ml vs. 19.81, 95% CI = = 17.02-22.60 ng/ml]. Vitamin D measurement between November and May was a risk factor for vitamin D deficiency ($P < 0.05$). The frequency of hypocalcemia and hypophosphatemia was not different between two groups of vitamin D. Further longitudinal studies are needed to investigate whether monitoring vitamin D status and supplementation in children with cancer might prevent future complications related to vitamin D deficiency.

http://www.ncbi.nlm.nih.gov/pubmed/27270075

“Evidence of a protective association between in utero vitamin D exposure and lower respiratory tract infection was found ...”

Abstract

CONTEXT

It is unclear how in utero vitamin D deficiency affects the extraskeletal health of children, despite the known risks for adverse pregnancy/birth outcomes.

OBJECTIVE

This systematic review seeks to assess the effect of in utero vitamin D exposure on childhood allergy and infection outcomes using the PRISMA guidelines.

DATA SOURCES

MEDLINE, Cochrane Library, and Web of Science databases were searched.

STUDY SELECTION

Literature published through April 2015 was searched for studies reporting on the association between maternal pregnancy or cord blood vitamin D status and childhood allergy and infection.

DATA EXTRACTION

Of 4175 articles identified, 43 studies met the inclusion criteria. They examined a wide variety of outcomes, using many different vitamin D cutoff values in their analyses.

DATA SYNTHESIS

For most outcomes, results were inconsistent, although there appeared to be a protective effect between higher in utero vitamin D status and childhood lower respiratory tract infection (5 of 10 studies).

CONCLUSIONS

More research is needed on childhood allergy and infection outcomes, and future studies should standardize outcome reporting, especially with regard to cutoff values for vitamin D concentrations. Evidence of a protective association between in utero vitamin D exposure and lower respiratory tract infection was found, while the other outcomes were either understudied or showed inconsistent results.

http://www.ncbi.nlm.nih.gov/pubmed/27083486

Nutrition Review • June 2016

Maternal and cord blood vitamin D status and childhood infection and allergic disease: a systematic review

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Obstetrics And Gynecology Clinics Of North America • June 2016

Evaluation of Anemia

Author information

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Abstract

“Anemia is a common problem in primary care. Classification based on mean cell volume narrows the differential diagnosis and directs testing. A marked macrocytosis is characteristic of vitamin B12 and folate deficiencies, certain medications, and primary bone marrow disorders. The three most common causes of microcytic anemia are iron deficiency, thalassemia trait, and anemia of inflammation. Additional laboratory testing is required for diagnosis. Determination of the rate of development of anemia and examination of a blood smear may provide diagnostic clues to guide more specialized testing. Diagnosis of iron, vitamin B12, or folate deficiency mandates determination of the underlying cause.”

http://www.ncbi.nlm.nih.gov/pubmed/27212091

“The leading causes of macrocytic anemia (number of patients, %) were myelodysplastic syndromes (121, 19.3 %), suspected bone marrow failure syndromes (BMF; 74, 11.8 %), aplastic anemia (51, 8.1 %), plasma cell dyscrasia (45, 7.2 %), and vitamin B12 deficiency (40, 6.4 %) in Tohoku University Hospital.”

International Journal Of Hematology • June 2016

Causes of macrocytic anemia among 628 patients: mean corpuscular volumes of 114 and 130 fL as critical markers for categorization

Author information

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Abstract

There have been no studies on the distribution of causes of macrocytic anemia with respect to mean corpuscular volume (MCV) cutoff values. We retrospectively investigated the causes of macrocytic anemia (MCV ≥100 fL) among 628 patients who visited the outpatient hematology clinic in Tohoku University Hospital. To ensure data validity, we also analyzed data from 307 patients in eight other hospitals in the Tohoku district. The leading causes of macrocytic anemia (number of patients, %) were myelodysplastic syndromes (121, 19.3 %), suspected bone marrow failure syndromes (BMF; 74, 11.8 %), aplastic anemia (51, 8.1 %), plasma cell dyscrasia (45, 7.2 %), and vitamin B12 deficiency (40, 6.4 %) in Tohoku University Hospital. We made three primary findings as follows. First, the most common cause of macrocytic anemia is BMF. Second, lymphoid and solid malignancies are also common causes of macrocytosis. Third, macrocytic anemia may be classified into three groups: Group 1 (megaloblastic anemia and medications), which can exceed MCV 130 fL; Group 2 (alcoholism/liver disease, BMF, myeloid malignancy, and hemolytic anemia), which can exceed MCV 114 fL; and Group 3 (lymphoid malignancy, chronic renal failure, hypothyroidism, and solid tumors), which does not exceed MCV 114 fL. These conclusions were supported by the results from eight other hospitals.

http://www.ncbi.nlm.nih.gov/pubmed/27352093

Rinsho Shinkeigaku • June 2016

A case of vitamin B12 deficiency with involuntary movements and bilateral basal ganglia lesions

Author information
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Abstract

“An 86-year-old woman with a one-year history of dementia was admitted to our hospital complaining of loss of appetite, hallucinations, and disturbance of consciousness. She gradually presented with chorea-like involuntary movements of the extremities. Diffusion-weighted magnetic resonance imaging (MRI) showed bilateral symmetrical hyperintense signals in the basal ganglia. The serum vitamin B12 level was below the lower detection limit of 50 pg/ml. The homocysteine level was markedly elevated at 115.8 nmol/ml. Anti-intrinsic factor and anti-parietal cell antibody tests were positive. Gastrointestinal endoscopy revealed atrophic gastritis. The patient was diagnosed with encephalopathy due to vitamin B12 deficiency caused by pernicious anemia. Involuntary movements and MRI abnormalities improved with parenteral vitamin B12 supplementation. Bilateral basal ganglia lesions are rare manifestations of adult vitamin B12 deficiency. The present case is considered valuable in identifying the pathophysiology of involuntary movement due to vitamin B12 deficiency.”

http://www.ncbi.nlm.nih.gov/pubmed/27356735

“Vitamin B12 is necessary for formation of red blood cells, DNA synthesis, neural myelination, brain development, and growth. Vitamin B12 deficiency is often asymptomatic early in its course; however, once it manifests, particularly with neurological symptoms, reversal by dietary changes or supplementation becomes less effective.”

Science Reports • June 2016

NutriPhone: a mobile platform for low-cost point-of-care quantification of vitamin B12 concentrations

Author information

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Abstract

Vitamin B12 is necessary for formation of red blood cells, DNA synthesis, neural myelination, brain development, and growth. Vitamin B12 deficiency is often asymptomatic early in its course; however, once it manifests, particularly with neurological symptoms, reversal by dietary changes or supplementation becomes less effective. Access to easy, low cost, and personalized nutritional diagnostics could enable individuals to better understand their own deficiencies as well as track the effects of dietary changes. In this work, we present the NutriPhone, a mobile platform for the analysis of blood vitamin B12 levels in 15 minutes. The NutriPhone technology comprises of a smartphone accessory, an app, and a competitive-type lateral flow test strip that quantifies vitamin B12 levels. To achieve the detection of sub-nmol/L physiological levels of vitamin B12, our assay incorporates an innovative “spacer pad” for increasing the duration of the key competitive binding reaction and uses silver amplification of the initial signal. We demonstrate the efficacy of our NutriPhone system by quantifying physiologically relevant levels of vitamin B12 and performing human trials where it was used to accurately evaluate blood vitamin B12 status of 12 participants from just a drop (~40 µl) of finger prick blood.

Full text, graphs, charts and 38 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4908584/

Clinical Medicine London • June 2016

The holistic management of consequences of cancer treatment by a gastrointestinal and nutrition team: a financially viable approach to an enormous problem?

Author information
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Abstract

“There is no national NHS tariff to fund services for patients experiencing long-term bowel and nutritional problems after cancer treatment. In this paper, we report the clinical characteristics and outcomes of patients referred to our service and the estimated cost of a completed episode of care. Patient characteristics, symptom severity, investigations, diagnoses, number of clinic visits and referrals elsewhere were recorded in a prospective cohort study. During 2013-14, 325 patients completed assessment and treatment. The majority of original cancer diagnoses were urological (43%) and gynaecological (21%). A median of six investigations were requested. 62% were found to have three or more new diagnoses including small intestinal bacterial overgrowth (46%), **vitamin D deficiency (38%)**, bile acid malabsorption (28%), gastritis (22%), radiation-induced bleeding (20%), **vitamin B12 deficiency (17%)**, pelvic floor weakness (17%), colorectal polyps (13%) and pancreatic insufficiency (5%). A median of three visits were required and all commonly reported gastrointestinal symptoms improved by discharge. The mean episode of care per patient was costed at £1,563. Effective amelioration of chronic gastrointestinal toxicity after cancer treatment costs substantially less than treating the cancer in the first place and requires an NHS tariff.”

http://www.ncbi.nlm.nih.gov/pubmed/27251913

Nutrition Reviews • July 2016

Safe use of high intakes of folic acid: research challenges and paths forward

Author information
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Abstract

"Adequate folic acid intake is an effective dietary-based prevention tool for reducing the risk of neural tube defects. Achieving adequate intake for the prevention of neural tube defects frequently requires the consumption of foods fortified with folic acid and/or the use of folic acid-containing dietary supplements. To date, research on the potential for adverse effects of high intakes of folic acid has been limited. Without such research, it is difficult to define a value for high intake. In May 2015, an expert panel was tasked with examining the available scientific literature and making research recommendations within 4 general categories of potential folate-related adverse health effects: cancer, cognition in conjunction with vitamin B12 deficiency, hypersensitivity-related outcomes, and thyroid and diabetes-related disorders. This article summarizes the expert panel's conclusions, outlines the challenges faced when reviewing the literature, and examines some of the panel's recommendations for research."

http://www.ncbi.nlm.nih.gov/pubmed/27272334

“In the elderly, even mild anaemia leads to significantly decreased quality of life and reduced survival rate. Therefore even mild anaemias should be worked up especially in the elderly. More than 75 % of all anaemias have a specific and treatable cause.”

Deutsch Medizinische Wochenschrift • July 2016

Anaemia In The Elderly

Leischker AH, Fetscher S, Kolb GF.

Abstract

In the elderly, even mild anaemia leads to significantly decreased quality of life and reduced survival rate. Therefore even mild anaemias should be worked up especially in the elderly. More than 75 % of all anaemias have a specific and treatable cause. Differential diagnosis of anaemia in the elderly is much more challenging compared to the differential diagnosis in younger patients: in older patients often more than one dysfunction is responsible for the anaemia simultaneously. Many routine laboratory parameters are changed by ageing and are therefore only of limited value for diagnosis of anaemia. Soluble transferinreceptor and hepcidin are two parameters feasible for differential diagnosis of the causes of anaemia in the elderly.The most common cause of iron deficiency anaemia in the elderly is gastrointestinal bleeding. Many causes for gastrointestinal bleeding -like angiodysplasia of the colon - can readily be treated with endoscopic therapy. For this reason, colonoscopy is part of the standard workup for elderly patients with iron-deficient anaemia (IDA) if no contraindications exist.Therapy of anaemia is based on the specific cause or the causes. In IDA, the first step other than causal treatment is to replace iron orally. If this is not tolerated because of side effects or does not lead to a sufficient rise in the haemoglobin level, intravenous iron replacement therapy is indicated. Folic acid deficiency is generally treated orally, whereas vitamin B12 deficiency is generally treated by the parenteral - preferably subcutaneous - route. In anaemia due to chronic renal failure and anaemia due to myelodysplastic syndromes, the underlying cause must be treated, furthermore erythropoiesis-stimulating agents can be indicated.

http://www.ncbi.nlm.nih.gov/pubmed/27359315

Biochimie • July 2016

Genetic animal models to decipher the pathogenic effects of vitamin B12 and folate deficiency

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Abstract

“Vitamin B12 and folate are essential micronutrients that provide methyl groups for cellular methylations through the so-called one-carbon metabolism. Deficits in the absorption and transport or defects of the enzymes can lead to human pathogenesis comprising hematologic, neural, gastrointestinal, hepatic, renal, cardiovascular and developmental manifestations. One-carbon metabolism is a complex, multistep and multi-organ metabolism, and the understanding of the mechanisms at work have benefited from human inborn errors and population studies, as well as from nutritional animal models. Since 15 years, a wide variety of genetically engineered mice has been developed and has proved to be useful to decipher the underlying mechanisms. These genetically engineered mice target all the genes that are important for the intestinal absorption, cellular transport and metabolism of vitamin B12 and folate, which are detailed in this article. In conclusion, these mouse models represent valuable experimental paradigms for human pathogenesis. Since no animal model recapitulates the full spectrum of a human disease, researchers have to choose the one that is the most relevant for their specific needs, and this review may help in this respect.”

http://www.ncbi.nlm.nih.gov/pubmed/27178438

“These and other data strongly imply that excessive intake of folic acid is not always safe in certain populations of different age and ethnical/genetic background.”

Biochimie • July 2016

Excessive folic acid intake and relation to adverse health outcome

Author information

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Abstract

The recent increase in the intake of folic acid by the general public through fortified foods and supplements, has raised safety concern based on early reports of adverse health outcome in elderly with low B12 status who took high doses of folic acid. These safety concerns are contrary to the 2015 WHO statement that “high folic acid intake has not reliably been shown to be associated with negative healeffects”. In the folic acid post-fortification era, we have shown that in elderly participants in NHANES 1999-2002, high plasma folate level is associated with exacerbation of both clinical (anemia and cognitive impairment) and biochemical (high MMA and high Hcy plasma levels) signs of vitamin B12 deficiency. Adverse clinical outcomes in association with high folate intake were also seen among elderly with low plasma B12 levels from the Framingham Original Cohort and in a study from Australia which combined three elderly cohorts. Relation between high folate and adverse biochemical outcomes were also seen in the Sacramento Area Latino Study on Aging (High Hcy, high MMA and lower TC2) and at an outpatient clinic at Yale University where high folate is associated with higher MMA in the elderly but not in the young. Potential detrimental effects of high folic acid intake may not be limited to the elderly nor to those with B12 deficiency. A study from India linked maternal high RBC folate to increased insulin resistance in offspring. Our study suggested that excessive folic acid intake is associated with lower natural killer cells activity in elderly women. In a recent study we found that the risk for unilateral retinoblastoma in offspring is 4 fold higher in women that are homozygotes for the 19 bp deletion in the DHFR gene and took folic acid supplement during pregnancy. In the elderly this polymorphism is associated with lower memory and executive scores, both being significantly worse in those with high plasma folate. These and other data strongly imply that excessive intake of folic acid is not always safe in certain populations of different age and ethnical/genetic background.

http://www.ncbi.nlm.nih.gov/pubmed/27131640

Pediatrics • January 2015

Core symptoms of autism improved after vitamin D supplementation

Author information

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Abstract

“Autism spectrum disorder (ASD) is a common neurodevelopmental disorder caused by a complex interaction between genetic and environmental risk factors. Among the environmental factors, vitamin D3 (cholecaliferol) seems to play a significant role in the etiology of ASD because this vitamin is important for brain development. Lower concentrations of vitamin D3 may lead to increased brain size, altered brain shape, and enlarged ventricles, which have been observed in patients with ASD. Vitamin D3 is converted into 25-hydroxyvitamin D3 in the liver. Higher serum concentrations of this steroid may reduce the risk of autism. Importantly, children with ASD are at an increased risk of vitamin D deficiency, possibly due to environmental factors. It has also been suggested that vitamin D3 deficiency may cause ASD symptoms. Here, we report on a 32-month-old boy with ASD and vitamin D3 deficiency. His core symptoms of autism improved significantly after vitamin D3 supplementation. This case suggests that vitamin D3 may play an important role in the etiology of ASD, stressing the importance of clinical assessment of vitamin D3 deficiency and the need for vitamin D3 supplementation in case of deficiency.”

Full text with 25 references

http://pediatrics.aappublications.org/content/135/1/e196.long

“These results demonstrated that obesity was a risk factor for vitamin D deficiency in all races, especially the Asian and black populations.”

Journal Of Community Hospital Internal Medicine Perspectives • February 2015

The incidence of vitamin D deficiency in the obese: a retrospective chart review

Author information
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Abstract

OBJECTIVE
To determine whether the obese population is more likely to be vitamin D deficient compared to healthy and overweight individuals.
PATIENTS AND METHODS
A retrospective chart review was performed for patients seen in two ambulatory clinics in South Florida over a 1-year period (n=402). Patients' vitamin D levels drawn during annual wellness visits were analyzed. Subjects were categorized based on body mass index (BMI) as normal (BMI <24.9), overweight (BMI 25.0-29.9), and obese (BMI >30.0). Their 25-OH vitamin D status was defined as normal (>30 ng/mL), insufficient (20.0-29.9 ng/mL), and deficient (<20 ng/mL). The study included both men and women of black, white, Hispanic, and Asian races. Other variables in the study included age, history of hypertension, and diabetes. Patients with conditions leading to vitamin D malabsorption (chronic pancreatitis, celiac disease, Crohn's disease, cystic fibrosis, ileocecal resection) were excluded. Patients with prior vitamin D supplementation were also excluded.
RESULTS
The results of the study indicated a significant association of vitamin D deficiency and obesity ($p<0.05$). Patients who were obese had a relative risk of 3.36 (95% CI: 1.50-7.54) for vitamin D deficiency compared to subjects with normal BMI. The study also showed a significant association between vitamin D levels and obesity when controlling for age, race, and presence of hypertension ($p <0.05$), with Asians and blacks more likely to be vitamin D deficient.
CONCLUSION
These results demonstrated that obesity was a risk factor for vitamin D deficiency in all races, especially the Asian and black populations. This suggests that physicians should screen for vitamin D deficiency in the obese populations, especially among Asian and black races.

Full text, graphs, charts and 12 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4318816/pdf/JCHIMP-5-26069.pdf

“Vitamin D is inexpensive, readily available and safe.
It may have beneficial effects in Autism spectrum disorder subjects,
especially when the final serum level is more than 40 ng/ml.”

Nutrition And Neuroscience • April 2015

Vitamin D status in autism spectrum disorders and the efficacy of vitamin D supplementation in autistic children

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Abstract

Objectives Autism spectrum disorder (ASD) is a developmental disorder characterized by pervasive deficits in social interaction, impairment in verbal and non-verbal communication, and stereotyped patterns of interests and activities. Vitamin-D deficiency was previously reported in autistic children. However, the data on the relationship between vitamin D deficiency and the severity of autism are limited. Methods We performed a case-controlled cross-sectional analysis conducted on 122 ASD children, to assess their vitamin D status compared to controls and the relationship between vitamin D deficiency and the severity of autism. We also conducted an open trial of vitamin D supplementation in ASD children. Results Fifty-seven percent of the patients in the present study had vitamin D deficiency, and 30% had vitamin D insufficiency. The mean 25-OHD levels in patients with severe autism were significantly lower than those in patients with mild/moderate autism. Serum 25-OHD levels had significant negative correlations with Childhood Autism Rating Scale (CARS) scores. Of the ASD group, 106 patients with low-serum 25-OHD levels (<30 ng/ml) participated in the open label trial. They received vitamin D3 (300 IU/kg/day not to exceed 5000 IU/day) for 3 months. Eighty-three subjects completed 3 months of daily vitamin D treatment. Collectively, 80.72% (67/83) of subjects who received vitamin D3 treatment had significantly improved outcome, which was mainly in the sections of the CARS and aberrant behavior checklist subscales that measure behavior, stereotypy, eye contact, and attention span. Conclusion: Vitamin D is inexpensive, readily available and safe. It may have beneficial effects in ASD subjects, especially when the final serum level is more than 40 ng/ml. Trial registration number UMIN-CTR Trial Number: R000016846.

http://www.ncbi.nlm.nih.gov/pubmed/25876214

“We detected a high proportion of pregnant women with deficient or insufficient vitamin D levels, especially in the months of October to May, in pregnant women with overweight and obesity, and the youngest.”

Nutricion Hospitalaria • April 2015

Prevalence of vitamin d deficiency and insuffiency and associated factors in pregnant women of northern Spain

Author information

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Abstract

BACKGROUND AND OBJECTIVES

The vitamin D deficiency during pregnancy has been associated with adverse events during pregnancy and the postnatal child development. In this study we examined plasma levels of vitamin D [25(OH)D3] and factors associated with plasma deficiency and insufficiency in pregnant women in northern Spain.

METHODS

We analyzed data from 453 pregnant women participating in the INMA-Asturias cohort in which was determined 25(OH)D3 by high resolution liquid chromatography.Dietary intake of vitamin D was estimated through a food frequency validated questionnaire. We estimated the prevalence of deficiency [25(OH)D3 <20 ng/ml] and insufficiency [20 to 29.9 ng / ml] of vitamin D and analyzed the distribution of 25(OH)D3 per month extraction and other factors.

RESULTS

The mean concentration of 25(OH)D3 was 27.7 ng/ml (range 6.4 to 69.5). 27.4% of pregnant women had deficient levels and 35.3% inssuficient. Levels of 25(OH)D3 were higher in the summer months (median 34.1 ng/ml). There was a higher percentage of deficiency in pregnant women with overweight/obesity (34.5%) and under 25 years (47.8%). The average daily intake of vitamin D was 5.48 mg / day (SD 2.82 range 1.09 to 32.52).Intake during the months of October to May was associated with levels of 25(OH)D3. 8.6% reported taking supplements of vitamin D.

CONCLUSIONS

We detected a high proportion of pregnant women with deficient or insufficient vitamin D levels, especially in the months of October to May, in pregnant women with overweight and obesity, and the youngest.

http://www.ncbi.nlm.nih.gov/pubmed/25795951

“Chronic use of acid-lowering agents is a risk factor for developing vitamin B12 deficiency.”

Internal Medicine Journal • April 2015

Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis

Author information

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Abstract

BACKGROUND

Vitamin B12 (cobalamin) deficiency can result in irreversible structural brain changes if not treated appropriately. Long-term use of acid-lowering agents (ALA) has been linked to vitamin B12 deficiency, but results are inconsistent.

AIM

To evaluate the association between prolonged ALA use and vitamin B12 deficiency by performing a meta-analysis.

METHODS

A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents, Cochrane Library, Google Scholar, Science Direct and Web of Science. Original data were abstracted from each study and used to calculate a pooled odds ratio and 95% confidence interval (95% CI).

RESULTS

Of the articles reviewed, four case-control studies (4254 cases and 19,228 controls) and one observational study met full criteria for analysis. The long-term ALA use was significantly associated with development of vitamin B12 deficiency (hazard ratio 1.83, 95% CI: 1.36-2.46, P-value 0.00).

CONCLUSION

Chronic use of ALA is a risk factor for developing vitamin B12 deficiency. Judicious prescribing of ALA and regular monitoring of vitamin B12 in patients who are inevitably on long-term ALA therapy are recommended.

http://www.ncbi.nlm.nih.gov/pubmed/25583062

“Vitamin B-12 deficiency was associated with risk of grade repetition and school absenteeism rates ...”

Journal Of Nutrition • July 2015

Vitamin B-12 Deficiency in Children Is Associated with Grade Repetition and School Absenteeism, Independent of Folate, Iron, Zinc, or Vitamin A Status Biomarkers

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Abstract

BACKGROUND
Micronutrients are essential to neurocognitive development; yet their role in educational outcomes is unclear.

OBJECTIVE
We examined the associations of micronutrient status biomarkers with the risk of grade repetition and rates of school absenteeism in a cohort of school children.

METHODS
We recruited 3156 children aged 5-12 y from public schools in Bogota, Colombia. Circulating ferritin, hemoglobin, zinc, vitamin A, and vitamin B-12; erythrocyte folate; and mean corpuscular volume (MCV) were measured in blood samples obtained at the beginning of the year. Absenteeism was recorded weekly during the school year, and grade repetition was determined the next year. Risk ratios for grade repetition and rate ratios for absenteeism were estimated by categories of micronutrient status indicators with use of Poisson regression, adjusting for potential confounders.

RESULTS
The risk of grade repetition was 4.9%, and the absenteeism rate was 3.8 d per child-year of observation. Vitamin B-12 deficiency (<148 pmol/L) was associated with an adjusted 2.36-fold greater risk of grade repetition (95% CI: 1.03, 5.41; P = 0.04) compared with plasma concentrations ≥148 pmol/L. Other micronutrients were not related to grade repetition. Vitamin B-12 deficiency was also associated with school absenteeism rates. Compared with children with plasma vitamin B-12 concentrations ≥148 pmol/L, vitamin B-12-deficient children had a 1.89-times higher adjusted rate (95% CI: 1.53, 2.34; P < 0.0001). Anemia was related to a 72% higher rate (95% CI: 48%, 99%; P < 0.0001), whereas every 5-fL difference in MCV was associated with a 7% lower adjusted rate (95% CI: 4%, 10%; P < 0.0001).

CONCLUSIONS
Vitamin B-12 deficiency was associated with risk of grade repetition and school absenteeism rates in school children from Bogota, Colombia. The effects of correcting vitamin B-12 deficiency on educational outcomes and neurocognitive development of school children need to be determined in intervention studies.

http://www.ncbi.nlm.nih.gov/pubmed/25972530

Preventive Nutrition And Food Science • September 2015

Low Nourishment of Vitamin C Induces Glutathione Depletion and Oxidative Stress in Healthy Young Adults

Author information
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Abstract

"The present study was conducted to assess the status of vitamin C among healthy young adults in relation to serum antioxidant parameters [glutathione (GSH), thiols, and total antioxidant capacity, (TAC)], and oxidative stress markers [malondialdehyde (MDA), and nitrites plus nitrates (NN)]. A prospective study included 200 young adults, and their dietary intake was assessed by using food diaries. Fasting plasma vitamin C, serum levels of GSH, thiols, TAC, MDA, and NN were measured using biochemical assays. It was observed that 38% of the enrolled subjects, n=76, had an adequate dietary intake of vitamin C (ADI group). Meanwhile, 62%, n=124, had a low dietary intake of vitamin C (LDI group) as compared to the recommended dietary allowances. The fasting plasma level of vitamin C was significantly higher in the ADI group as compared to the LDI group. Oxidative stress in the sera of the LDI group was evidenced by depletion of GSH, low thiols levels, impairment of TAC, an elevation of MDA, and increased NN. In the ADI group, positive correlations were found between plasma vitamin C and serum antioxidant parameters (GSH, thiols, and TAC). Meanwhile, the plasma vitamin C was negatively correlated with serum MDA and NN levels. **This study reveals a significant increase of oxidative stress status and reduced antioxidant capacity in sera from healthy young adults with low intake of the dietary antioxidant, vitamin C.**"

Full text, graphs, charts and 26 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4596346/

“These findings suggest that the four weeks of multi-vitamin and mineral supplementation may have beneficial effects on mood, underpinned by elevated B-vitamins and lowered homocysteine in healthy young adults.”

Nutrients • October 2015

Effects of Four-Week Supplementation with a Multi-Vitamin/Mineral Preparation on Mood and Blood Biomarkers in Young Adults: A Randomised, Double-Blind, Placebo-Controlled Trial

Author information

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Abstract

This study explored the effects of four-week multi-vitamin and mineral (MVM) supplementation on mood and neurocognitive function in healthy, young adults. Fifty-eight healthy adults, 18-40 years of age (M = 25.82 years, SD = 4.87) participated in this randomised, double-blind, placebo-controlled trial, in which mood and blood biomarkers were assessed at baseline and after four weeks of supplementation. Compared to placebo, MVM supplementation was associated with significantly lowered homocysteine and increased blood B-vitamin levels ($p < 0.01$). MVM treatment was also associated with significantly improved mood, as measured by reduced scores on the “depression-dejection” subscale of the Profile of Mood States ($p = 0.018$). These findings suggest that the four weeks of MVM supplementation may have beneficial effects on mood, underpinned by elevated B-vitamins and lowered homocysteine in healthy young adults.

Full text, graphs, charts and 51 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4663579/

Journal AOAC International • November 2015

Determination of Vitamin B12 in Infant, Adult, and Pediatric Formulas by HPLC-UV and Column Switching: Collaborative Study Final Action 2011.10.

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Abstract

AOAC First Action Method 2011.10, Vitamin B12 in Infant and Pediatric Formulas and Adult Nutritionals, was collaboratively studied. This method uses a pH 4.5 sodium acetate buffer and potassium cyanide at 105°C to extract and convert all biologically active forms of vitamin B12 present to cyanocobalamin; octylsilyl (C8) or C18 SPE cartridges to purify and concentrate cyanocobalamin; a combination of size-exclusion and RPLC to isolate cyanocobalamin; and visible absorbance at 550 nm to detect and quantitate cyanocobalamin in infant, pediatric, and adult nutritionals with vitamin B12 concentrations greater than 0.025 µg/100 g ready-to-feed (RTF) liquid. During this collaborative study, nine to 11 laboratories from eight different countries analyzed blind duplicates of 12 infant, pediatric, and adult nutritional formulas. Per the AOAC Expert Review Panel (ERP) on Stakeholder Panel on Infant Formula and Adult Nutritionals (SPIFAN) Nutrient Methods the method demonstrated acceptable repeatability and reproducibility and met SPIFAN Standard Method Performance Requirements (SMPRs®) for the majority of product matrixes analyzed. Vitamin B12 SPIFAN SMPRs for repeatability were ≤15% RSD at vitamin B12 concentrations of 0.01 µg/100 g RTF liquid and ≤7% RSD at vitamin B12 concentrations of 0.2-5.0 µg/100 g RTF liquid. Vitamin B12 SPIFAN SMPRs for reproducibility were ≤11% RSD in products with vitamin B12 concentrations ranging from 0.3 to 5.0 µg/100 g RTF liquid. During this collaborative study, the RSDr ranged from 2.98 to 9.77%, and the RSDR ranged from 3.54 to 19.5%. During previous single-laboratory validation studies, the method LOQ was estimated to be 0.025 µg/100 g RTF liquid.

http://www.ncbi.nlm.nih.gov/pubmed/

“Vitamin B12 deficiency is common in the general population, its causes and origins are multiple, we list them in order of occurrence: Biermer disease, the FCS, and the intake deficiency in our population.”

La Tunisie Medicale • November 2015

Causes of vitamin B12 deficiency

Belghith A, Mahjoub S, Ben Romdhane N.

Abstract

BACKGROUND

B12 Vitamin deficiency is common in adults (20% of general population of industrialized populations), especially in elderly patients (30-40%). The etiologies of Vitamin B12 deficiency have been dominated by the cobalamin syndrome nutrient and the Biermer disease, rarely by the intake or nutritional deficiency and bad absorptions.

STUDY OBJECTIVE

Establish an etiology of vitamin B12 in a Tunisian population Methods: In a prospective study involving 100 patients with macrocytic anemia, a comprehensive assessment has been carried out of: B12 vitamin and folate intake, homocysteine, immunological assessment (antibodies, intrinsic anti-factor and anti-gastric parietal cells), an endoscopic exploration, and a dietary nutritional survey.

RESULTS

The mean age of patients was 53.6 ± 17,6 years (13 - 88 years), the gender ratio (female/male) is 1.22. The clinical symptomatology shows a functional anemia syndrome in 89% of cases, a digestive syndrome in 88% of cases, and neurological disorders in 67% of cases. The intake of B12 vitamin was reduced (<180 pg/ml) in 99 patients, associated with a hyperhomocysteinemia in 81.63% of cases. The intrinsic anti-factor antibodies were positives in 32 patients, and the antibody anti-gastric parietal cells in 85 patients. Gastric biopsy was performed in 54 patients, showing a chronic atrophic gastritis of fundic localization in 44 patients, antral in 5 patients and pan- gastric in 3 patients. The diagnosis of Biermer anemia was held in 75% of patients, that of FCS in 16% of patients, and a lack of intake in 8% of patients. The etiology was undetermined in 1% of cases.

CONCLUSION

Vitamin B12 deficiency is common in the general population, its causes and origins are multiple, we list them in order of occurrence: Biermer disease, the FCS, and the intake deficiency in our population.

http://www.ncbi.nlm.nih.gov/pubmed/27126423

Journal Of Digestive Disorders • November 2015

Vitamin D deficiency in patients with intestinal malabsorption syndromes—think in and outside the gut

Author information
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Abstract

“There is a very high prevalence of vitamin D deficiency, which is defined by a serum level of 25-hydroxyvitamin D [25(OH)D] of lower than 20 ng/mL, in all populations of the world. Unfortunately, the prevalence of vitamin D deficiency in patients with intestinal malabsorption syndromes, including cystic fibrosis (CF), celiac disease (CD), short bowel syndrome and inflammatory bowel disease (IBD), is higher than that in the general population, indicating the presence of disease-specific causative factors. In this review, we aimed to present clinical findings to highlight the roles of insufficient exposure to sunlight and inflammation in the development of vitamin D deficiency in patients with intestinal malabsorption syndromes. Furthermore, we aimed to present experimental evidence that supported a role of vitamin D deficiency in the pathogenesis of IBD. Finally, we reviewed clinical intervention strategies aiming to normalize vitamin D status in and even to improve the conditions of patients and to discuss certain issues that needed to be addressed in future research.”

http://www.ncbi.nlm.nih.gov/pubmed/26316334

Ginekologia Polska • December 2015

Folate metabolism—epigenetic role of choline and vitamin B12 during pregnancy

By K. Drews

Abstract

"Adequate choline intake during pregnancy is essential for proper fetal development. Nowadays studies suggest that even in high income countries regular pregnant women diet does not provide the satisfactory amount of choline. Choline demand during pregnancy is high and it seems to exceed present choline intake recommendations. Moreover lactation period also demands choline supplementation because of its high concentration in female milk. Numerous studies on animal model proved correlation between choline supplementation during pregnancy and proper fetal cognitive function development. Despite increased synthesis in maternal liver during pregnancy choline demand is much higher than common dietary uptake. Nowadays studies as to the nutritional recommendations during pregnancy concern also vitamin B12 supplementation. Vitamin B12 deficiency may be an important risk factor of neural tube defects development. Presented article contains a review of data on proper choline and vitamin B12 uptake during pregnancy and lactation and potential results of choline and vitamin B12 poor maternal status."

http://www.ncbi.nlm.nih.gov/pubmed/26995945

Bonekey Reports • February 2014

Vitamin D: direct effects of vitamin D metabolites on bone: lessons from genetically modified mice

Author information

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Abstract

"The vitamin D endocrine system has clear beneficial effects on bone as demonstrated by prevention of rickets in children and by reducing the risk of osteomalacia or osteoporosis in adults or elderly subjects. Depending on the design of the study of genetically modified animals, however, 1,25(OH)2D and the vitamin D receptor (VDR) may have no effect, beneficial or even deleterious direct effects on bone. We present here a comprehensive model of the direct effects of vitamin D on bone. In case of sufficient calcium supply, vitamin D and its metabolites can improve the calcium balance and facilitate mineral deposition in bone matrix largely without direct effects on bone cells, although some beneficial effects may occur via mature osteoblasts, as demonstrated in mice with osteoblast-specific overexpression of VDR or 1α-hydroxylase. In case of calcium deficiency, however, 1,25(OH)2D enhances bone resorption, whereas simultaneously inhibiting bone mineralization, so as to defend serum calcium homeostasis at the expense of bone mass. This dual role probably provides a survival benefit for land vertebrates living in a calcium-poor environment."

Full text, graphs, charts and 51 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3944130/

Lab On A Chip • February 2014

Cholesterol testing on a smartphone

Author information

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Abstract

“Home self-diagnostic tools for blood cholesterol monitoring have been around for over a decade but their widespread adoption has been limited by the relatively high cost of acquiring a quantitative test-strip reader, complicated procedure for operating the device, and inability to easily store and process results. To address this we have developed a smartphone accessory and software application that allows for the quantification of cholesterol levels in blood. Through a series of human trials we demonstrate that the system can accurately quantify total cholesterol levels in blood within 60 s by imaging standard test strips. In addition, we demonstrate how our accessory is optimized to improve measurement sensitivity and reproducibility across different individual smartphones. With the widespread adoption of smartphones and increasingly sophisticated image processing technology, accessories such as the one presented here will allow cholesterol monitoring to become more accurate and widespread, greatly improving preventive care for cardiovascular disease.”

http://www.ncbi.nlm.nih.gov/pubmed/24336861

Lab On A Chip • April 2014

A smartphone platform for the quantification of vitamin D levels

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Abstract

“Vitamin D deficiency has been linked to a number of diseases and adverse outcomes including: osteoporosis, infections, diabetes, cardiovascular diseases, and even cancer. At present the vast majority of vitamin D testing is performed in large-scale laboratories at the request of a physician as part of an annual panel of blood tests. Here we present a system for rapid quantification of vitamin D levels on a smartphone. The system consists of a smartphone accessory, an app, and a test strip that allows the colorimetric detection of 25-hydroxyvitamin D using a novel gold nanoparticle-based immunoassay. We show that the system can be used to accurately measure physiological levels of 25-hydroxyvitamin D with accuracy better than 15 nM and a precision of 10 nM. We compare our system with well-established ELISA test kits for serum samples of unknown concentration and demonstrate equivalency of the results. We envision this as the first step towards the development of the NutriPhone, a comprehensive system for the analysis of multiple vitamins and micronutrients on a smartphone.”

http://www.ncbi.nlm.nih.gov/pubmed/24569647

“... with few exceptions, the reviewed studies documented relatively high deficiency prevalence among vegetarians. Vegans who do not ingest vitamin B12 supplements were found to be at especially high risk. Vegetarians, especially vegans, should give strong consideration to the use of vitamin B12 supplements to ensure adequate vitamin B12 intake. Vegetarians, regardless of the type of vegetarian diet they adhere to, should be screened for vitamin B12 deficiency.”

European Journal Of Clinical Nutrition • May 2014

The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature

Author information

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Abstract

Individuals following vegetarian diets are at risk for developing vitamin B12 deficiency owing to suboptimal intake. As vitamin B12 is essential for the synthesis of nucleic acids, erythrocytes and in the maintenance of myelin, deficiency may result in a variety of symptoms. Some of these symptoms may be severe while others may be irreversible. The objective of this review was to assess vitamin B12 deficiency, based on reported serum vitamin B12, among individuals adhering to different types of vegetarian diets. A systematic literature search was carried out using multiple search engines including PubMed, Medline, CINAHL plus, ERIC, Nursing and Allied Health Collection and Nursing/Academic Edition. The inclusion criteria consisted of original studies that assessed serum vitamin B12, studies written in English, non-case studies and studies that reported actual percentages of vitamin B12 deficiency. Forty research studies were included. The deficiency prevalence among infants reached 45%. The deficiency among the children and adolescents ranged from 0 to 33.3%. Deficiency among pregnant women ranged from 17 to 39%, dependent on the trimester. Adults and elderly individuals had a deficiency range of 0-86.5%. Higher deficiency prevalence was reported in vegans than in other vegetarians. Thus, with few exceptions, the reviewed studies documented relatively high deficiency prevalence among vegetarians. Vegans who do not ingest vitamin B12 supplements were found to be at especially high risk. Vegetarians, especially vegans, should give strong consideration to the use of vitamin B12 supplements to ensure adequate vitamin B12 intake. Vegetarians, regardless of the type of vegetarian diet they adhere to, should be screened for vitamin B12 deficiency.

http://www.ncbi.nlm.nih.gov/pubmed/24667752

“Our findings suggest that vitamin D deficiency at birth is associated with increased risk of Lower respiratory tract infections particularly in infants born to mothers without allergy. The association seems strongest in infants born in fall.”

European Journal Of Epidemiology • August 2014

Cord blood 25(OH)D levels and the subsequent risk of lower respiratory tract infections in early childhood: the Ulm birth cohort

Author information

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Abstract

Lower respiratory tract infections (LRTIs) are a major cause of hospitalization in infants. Research suggests that immunomodulatory properties of vitamin D may influence LRTI risk. This study's objective was to examine whether 25-hydroxyvitamin D [25(OH)D] concentrations in cord blood influenced susceptibility to LRTI in the first year of life. Data was analyzed from a prospective birth cohort of 777 mother-infant pairs based in Ulm, Germany. Relative risks (RRs) of LRTI in relation to 25(OH)D cord blood levels were estimated by log-binomial regression after adjustment for potential confounders. To account for seasonal variation in both vitamin D levels and infections, we examined the association in different seasons. Analyses were conducted using clinical predefined cutpoints, quartiles, and season-standardized 25(OH)D quartiles. We observed a statistically significant association between 25(OH)D status in cord blood and risk of LRTI across the year using clinical cutpoints. The adjusted RR of LRTI for individuals with vitamin D deficiency (<25 nmol/L) in comparison to the referent category (>50 nmol/L) was 1.32 [95 % confidence interval (CI) 1.00, 1.73]. The association differed by maternal allergy status; children born to mothers without allergy demonstrated a RR of 1.45 (95 % CI 1.03, 2.03). The effect was largely driven by a strong association between 25(OH)D and LRTI in infants born in fall with a RR of 3.07 (95 % CI 1.37, 6.87). Our findings suggest that vitamin D deficiency at birth is associated with increased risk of LRTI particularly in infants born to mothers without allergy. The association seems strongest in infants born in fall.

http://www.ncbi.nlm.nih.gov/pubmed/24859820

“Lower plasma folate status during pregnancy was associated with antenatal depression, but not with postnatal depression.”

Journal Of Psychiatric Research • August 2014

Relationships of maternal folate and vitamin B12 status during pregnancy with perinatal depression: The GUSTO study

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Abstract

Studies in the general population have proposed links between nutrition and depression, but less is known about the perinatal period. Depletion of nutrient reserves throughout pregnancy and delayed postpartum repletion could increase the risk of perinatal depression. We examined the relationships of plasma folate and vitamin B12 concentrations during pregnancy with perinatal depression. At 26th-28th weeks of gestation, plasma folate and vitamin B12 were measured in women from the GUSTO mother-offspring cohort study in Singapore. Depressive symptoms were measured with the Edinburgh Postnatal Depression Scale (EPDS) during the same period and at 3-month post-partum. EPDS scores of ≥15 during pregnancy or ≥13 at postpartum were indicative of probable depression. Of 709 women, 7.2% (n = 51) were identified with probable antenatal depression and 10.4% (n = 74) with probable postnatal depression. Plasma folate concentrations were significantly lower in those with probable antenatal depression than those without (mean ± SD; 27.3 ± 13.8 vs 40.4 ± 36.5 nmol/L; p = 0.011). No difference in folate concentrations was observed in those with and without probable postnatal depression. In adjusted regression models, the likelihood of probable antenatal depression decreases by 0.69 for every unit variation (increase) in folate (OR = 0.69 per SD increase in folate; 95% CI: 0.52, 0.94). Plasma vitamin B12 concentrations were not associated with perinatal depression. Lower plasma folate status during pregnancy was associated with antenatal depression, but not with postnatal depression. Replication in other studies is needed to determine the direction of causality between low folate and antenatal depression.

http://www.ncbi.nlm.nih.gov/pubmed/24774647

“Both low sodium intakes and high sodium intakes are associated with increased mortality, consistent with a U-shaped association between sodium intake and health outcomes.”

American Journal Of Hypertension • September 2014

Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis

Author information

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Abstract

BACKGROUND

The effect of sodium intake on population health remains controversial. The objective was to investigate the incidence of all-cause mortality (ACM) and cardiovascular disease events (CVDEs) in populations exposed to dietary intakes of low sodium (<115 mmol), usual sodium (low usual sodium: 115-165 mmol; high usual sodium: 166-215 mmol), and high sodium (>215 mmol).

METHODS

The relationship between individual measures of dietary sodium intake vs. outcome in cohort studies and randomized controlled trials (RCTs) measured as hazard ratios (HRs) were integrated in meta-analyses.

RESULTS

No RCTs in healthy population samples were identified. Data from 23 cohort studies and 2 follow-up studies of RCTs (n = 274,683) showed that the risks of ACM and CVDEs were decreased in usual sodium vs. low sodium intake (ACM: HR = 0.91, 95% confidence interval (CI) = 0.82-0.99; CVDEs: HR = 0.90, 95% CI = 0.82-0.99) and increased in high sodium vs. usual sodium intake (ACM: HR = 1.16, 95% CI = 1.03-1.30; CVDEs: HR = 1.12, 95% CI = 1.02-1.24). In population representative samples adjusted for multiple confounders, the HR for ACM was consistently decreased in usual sodium vs. low sodium intake (HR = 0.86; 95% CI = 0.81-0.92), but not increased in high sodium vs. usual sodium intake (HR = 1.04; 95% CI = 0.91-1.18). Within the usual sodium intake range, the number of events was stable (high usual sodium vs. low usual sodium: HR = 0.98; 95% CI = 0.92-1.03).

CONCLUSIONS

Both low sodium intakes and high sodium intakes are associated with increased mortality, consistent with a U-shaped association between sodium intake and health outcomes.

http://www.ncbi.nlm.nih.gov/pubmed/24651634

Neuroscience And Biobehavioral Reviews • November 2014

B vitamin polymorphisms and behavior: evidence of associations with neurodevelopment, depression, schizophrenia, bipolar disorder and cognitive decline

Author information

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Abstract

“The B vitamins folic acid, vitamin B12 and B6 are essential for neuronal function, and severe deficiencies have been linked to increased risk of neurodevelopmental disorders, psychiatric disease and dementia. Polymorphisms of genes involved in B vitamin absorption, metabolism and function, such as methylene tetrahydrofolate reductase (MTHFR), cystathionine ß synthase (CßS), transcobalamin 2 receptor (TCN2) and methionine synthase reductase (MTRR), have also been linked to increased incidence of psychiatric and cognitive disorders. However, the effects of these polymorphisms are often quite small and many studies failed to show any meaningful or consistent associations. This review discusses previous findings from clinical studies and highlights gaps in knowledge. Future studies assessing B vitamin-associated polymorphisms must take into account not just traditional demographics, but subjects’ overall diet, relevant biomarkers of nutritional status and also analyze related genetic factors that may exacerbate behavioral effects or nutritional status.”

http://www.ncbi.nlm.nih.gov/pubmed/25173634

“Micronutrient deficiencies including iron and vitamin B12, and apparent excess of folate are present in educated Australian female students of childbearing age, including those studying nutrition.”

Nutrients • November 2014

Micronutrient status in female university students: iron, zinc, copper, selenium, vitamin B12 and folate

Author information

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Abstract

Young women are at an increased risk of micronutrient deficiencies, particularly due to higher micronutrient requirements during childbearing years and multiple food group avoidances. The objective of this study was to investigate biomarkers of particular micronutrients in apparently healthy young women. Female students (n = 308; age range 18-35 year; Body Mass Index 21.5 ± 2.8 kg/m2; mean ± SD) were recruited to participate in a cross-sectional study. Blood samples were obtained from participants in the fasted state and analysed for biomarkers of iron status, vitamin B12, folate, homocysteine, selenium, zinc, and copper. The results show iron deficiency anaemia, unspecified anaemia, and hypoferritinemia in 3%, 7% and 33.9% of participants, respectively. Low vitamin B12 concentrations (<120 pmol/L) were found in 11.3% of participants, while 4.7% showed sub-clinical deficiency based on serum methylmalonic acid concentrations >0.34 µmol/L. Folate concentrations below the reference range were observed in 1.7% (serum) or 1% (erythrocytes) of participants, and 99.7% of the participant had erythrocyte-folate concentrations >300 nmol/L. Serum zinc concentrations <10.7 µmol/L were observed in 2% of participants. Serum copper and selenium concentrations were below the reference range in 23% and 11% of participants, respectively. Micronutrient deficiencies including iron and vitamin B12, and apparent excess of folate are present in educated Australian female students of childbearing age, including those studying nutrition. The effects of dietary behaviours and food choices on markers of micronutrient status require further investigation.

http://www.ncbi.nlm.nih.gov/pubmed/25401503

Journal Of Nutrition, Health And Aging • December 2014

Nutritional status of the elderly in rural North China: a cross-sectional study

Author information
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Abstract

OBJECTIVES
This study aimed to describe the nutritional status of elderly people living in a rural area of North China.
DESIGN
Community-based, cross-sectional prevalence survey.
SETTING
3 rural towns of Lvliang City, Shanxi Province, China.
PARTICIPANTS
A sample of 1845 community residents (29.1% of those eligible) 55 years or older (birth before 1958-01-01).
MEASUREMENTS
The participants were assessed regarding demographic characteristics, height, weight, as well as having a physical examination and blood sampling for serum cholesterol, total homocysteine (tHcy), folate, and vitamin B12 levels.
RESULTS
991 (53.7%) were female and 139 (7.5%) did not complete the anthropometric measurement. Prevalence of underweight and obesity was 3.5% and 24.9% in men and 6.7% and 31.0% in women ($P = 0.003$, $P = 0.005$, respectively). Prevalence of hypercholesterolemia and hypocholesterolemia was 13.5% and 52.6% in men and 25.0% and 34.3% in women ($P < 0.001$, $P < 0.001$, respectively). Prevalence of high LDL-c concentrations was 8.8% in men and 16.8% in women ($P < 0.001$). The mean serum tHcy in men (28.8 ± 20.1 μmmol/l) was significantly higher than in women (21.0 ± 15.1 μmmol/L, $P < 0.001$). Prevalence of hyperhomocysteinemia (defined as > 15μmmol/L) was 79.7% in men and 65.5% in women ($P < 0.001$). Prevalence of low folate (defined as < 11 nmol/L) and vitamin B12 levels (defiend as < 185 pmol/L) was 70.8 % and 76.8% in men and 56.5% and 72.6% in women ($P < 0.001$, $P = 0.036$, respectively). Correlation coefficients between tHcy, folate, and vitamin B12 indicated an inverse linear correlation ($r = -0.21$, $P < 0.001$, $r = -0.35$, $P < 0.001$, respectively).
CONCLUSIONS
As China's economic climate has developed, the nutritional status of elderly people in the rural parts of the country has improved in some aspects. However, the trend toward obesity will lead to a shift in the burden of obesity-related chronic diseases. In addition, rurally-located elderly people are at high risk of death that may be associated with abnormal serum cholesterol. The data also suggest that severe deficiencies in folate and vitamin B12 levels exist, as well as there being a high prevalence of hyperhomocysteinemia. Folate and vitamin B12 supplementation are necessary to prevent related diseases.

http://www.ncbi.nlm.nih.gov/pubmed/25286452

"As China's economic climate has developed, the nutritional status of elderly people in the rural parts of the country has improved in some aspects.

However, the trend toward obesity will lead to a shift in the burden of obesity-related chronic diseases. In addition, rurally-located elderly people are at high risk of death that may be associated with abnormal serum cholesterol.

The data also suggest that severe deficiencies in folate and vitamin B12 levels exist, as well as there being a high prevalence of hyperhomocysteinemia. Folate and vitamin B12 supplementation are necessary to prevent related diseases."

Journal Of The American College Of Nutrition • January 2013

Calcium and vitamin D disparities are related to gender, age, race, household income level, and weight classification but not vegetarian status in the United States: Analysis of the NHANES 2001-2008 data set

Author information
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Abstract

OBJECTIVE

Adequate calcium and vitamin D intakes are critical during all life cycle stages. This study aimed to characterize usual intakes of calcium and vitamin D from food and dietary supplements in specific subpopulations of Americans so that fortification/enrichment and supplementation efforts may be targeted toward populations who are truly in need.

METHODS

The National Cancer Institute method was used to estimate usual intakes of calcium and vitamin D by source and compared usual intakes to the established Dietary Reference Intakes for U.S. residents aged ≥4 years using National Health and Nutrition Examination Survey 2001-2002, 2003-2004, 2005-2006, and 2007-2008 data sets.

RESULTS

These results showed for the first time that low-income, overweight, and/or obese minority populations may be at greater risk of calcium and vitamin D insufficiency. Children aged 4-8 years were more likely to obtain recommended dairy intakes compared with older children and adults of all ages. Food intakes of calcium decreased with age in adults. Adults who used supplemental calcium showed a lower prevalence of insufficiency. Calcium and vitamin D intakes from food and dietary supplements were not related to vegetarian status. Excessive intakes of calcium and vitamin D above the tolerable upper intake level were low among all studied populations and "overnutrification" was not widely present across these analyses.

CONCLUSIONS

Age- and gender-specific supplementation and modest use of fortification with calcium and vitamin D may be warranted for targeting certain subpopulations, particularly older adults, teenagers, minorities, and those who are low income and overweight and/or obese.

PRACTICAL APPLICATION

This study aimed to characterize usual intakes of calcium and vitamin D from food and dietary supplements in specific subpopulations of Americans so that fortification/enrichment and supplementation efforts may be better targeted. Low-income, overweight, and/or obese minority populations may be at a greater risk of calcium and vitamin D insufficiency.

http://www.ncbi.nlm.nih.gov/pubmed/24219375

"This study aimed to characterize usual intakes of calcium and vitamin D from food and dietary supplements in specific subpopulations of Americans so that fortification/enrichment and supplementation efforts may be better targeted.

Low-income, overweight, and/or obese minority populations may be at a greater risk of calcium and vitamin D insufficiency."

Nutrition Reviews • February 2013

How prevalent is vitamin B(12) deficiency among vegetarians?

Author information
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Abstract

"Vegetarians are at risk for vitamin B(12) (B12) deficiency due to suboptimal intake. The goal of the present literature review was to assess the rate of B12 depletion and deficiency among vegetarians and vegans. Using a PubMed search to identify relevant publications, 18 articles were found that reported B12 deficiency rates from studies that identified deficiency by measuring methylmalonic acid, holo-transcobalamin II, or both. The deficiency rates reported for specific populations were as follows: 62% among pregnant women, between 25% and almost 86% among children, 21-41% among adolescents, and 11-90% among the elderly. Higher rates of deficiency were reported among vegans compared with vegetarians and among individuals who had adhered to a vegetarian diet since birth compared with those who had adopted such a diet later in life. The main finding of this review is that vegetarians develop B12 depletion or deficiency regardless of demographic characteristics, place of residency, age, or type of vegetarian diet. Vegetarians should thus take preventive measures to ensure adequate intake of this vitamin, including regular consumption of supplements containing B12."

http://www.ncbi.nlm.nih.gov/pubmed/23356638

“The World Health Organization estimates that more than 2 billion people are deficient in key vitamins and minerals. Groups most vulnerable to these micronutrient deficiencies are pregnant and lactating women and young children, given their increased demands.

Systematic Reviews • August 2013

Micronutrient fortification of food and its impact on woman and child health: a systematic review

Author information
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Abstract

BACKGROUND

Vitamins and minerals are essential for growth and metabolism. The World Health Organization estimates that more than 2 billion people are deficient in key vitamins and minerals. Groups most vulnerable to these micronutrient deficiencies are pregnant and lactating women and young children, given their increased demands. Food fortification is one of the strategies that has been used safely and effectively to prevent vitamin and mineral deficiencies.

METHODS

A comprehensive search was done to identify all available evidence for the impact of fortification interventions. Studies were included if food was fortified with a single, dual or multiple micronutrients and impact of fortification was analyzed on the health outcomes and relevant biochemical indicators of women and children. We performed a meta-analysis of outcomes using Review Manager Software version 5.1.

RESULTS

Our systematic review identified 201 studies that we reviewed for outcomes of relevance. Fortification for children showed significant impacts on increasing serum micronutrient concentrations. Hematologic markers also improved, including hemoglobin concentrations, which showed a significant rise when food was fortified with vitamin A, iron and multiple micronutrients. Fortification with zinc had no significant adverse impact on hemoglobin levels. Multiple micronutrient fortification showed non-significant impacts on height for age, weight for age and weight for height Z-scores, although they showed positive trends. The results for fortification in women showed that calcium and vitamin D fortification had significant impacts in the post-menopausal age group. Iron fortification led to a significant increase in serum ferritin and hemoglobin levels in women of reproductive age and pregnant women. Folate fortification significantly reduced the incidence of congenital abnormalities like neural tube defects without increasing the incidence of twinning. The number of studies pooled for zinc and multiple micronutrients for women were few, though the evidence suggested benefit. There was a dearth of evidence for the impact of fortification strategies on morbidity and mortality outcomes in women and children.

CONCLUSION

Fortification is potentially an effective strategy but evidence from the developing world is scarce. Programs need to assess the direct impact of fortification on morbidity and mortality.

Full text, graphs, charts and 231 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3765883/

“A 25(OH)D level of 30 ng/mL is associated with optimal cardioprotection in children.”

Journal Of Pediatrics, Endocrinology And Metabolism • September 2013

Vitamin D status is associated with early markers of cardiovascular disease in prepubertal children

Nwosu BU, Maranda L, Cullen K, Ciccarelli C, Lee MM.

Abstract

BACKGROUND

The associations of 25-hydroxyvitamin D [25(OH)D], non-high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL), and related markers of early cardiovascular disease (CVD) are unclear in prepubertal children.

OBJECTIVE

To investigate the association of 25(OH)D with markers of CVD. The hypothesis was that 25(OH)D would vary inversely with non-HDL-C.

SUBJECTS AND METHODS

A prospective cross-sectional study of children (n=45; 26 males, 19 females) of mean age 8.3 ± 2.5 years to investigate the relationships between 25(OH)D and glucose, insulin, high-sensitivity C-reactive protein, and lipids. Vitamin D deficiency was defined as 25(OH)D <20 ng/mL; overweight as body mass index (BMI) ≥ 85 th but <95th percentile; and obesity as BMI >95th percentile.

RESULTS

Twenty subjects (44.4%) had BMI <85%, and 25 had BMI of ≥ 85%. Eleven participants (24.4%) had 25(OH)D of <20 ng/mL, and 10 (22.2%) had 25(OH)D of >30 ng/mL. Patients with 25(OH)D of <20 ng/mL had significantly elevated non-HDL-C (136.08 ± 44.66 vs. 109.88 ± 28.25, p=0.025), total cholesterol (TC)/HDL ratio (3.89 ± 1.20 vs. 3.21 ± 0.83, p=0.042), and triglycerides (TG) (117.09 ± 71.27 vs. 73.39 ± 46.53, p=0.024), while those with 25(OH)D of >30 ng/mL had significantly lower non-HDL-C, TC/HDL, TG, and LDL (82.40 ± 18.03 vs. 105.15 ± 28.38, p=0.006). Multivariate analysis showed significant inverse correlations between 25(OH)D and non-HDL cholesterol (ß=-0.337, p=0.043), and TC/HDL ratio (ß=-0.339, p=0.028), and LDL (ß=-0.359, p=0.016), after adjusting for age, race, sex, BMI, and seasonality.

CONCLUSIONS

Vitamin D varied inversely with non-HDL, TC/HDL, and LDL. A 25(OH)D level of 30 ng/mL is associated with optimal cardioprotection in children.

http://www.ncbi.nlm.nih.gov/pubmed/23817598

Ontario Health Technology Assessment Service • November 2013

Vitamin B12 intramuscular injections versus oral supplements: a budget impact analysis

By L. Masucci and R. Goeree

Abstract

BACKGROUND

Vitamin B12 deficiency can lead to adverse health effects such as anemia and, in some cases, permanent neurologic damage. In Canada, patients with vitamin B12 deficiency are typically given intramuscular injections, which incur considerable cost and inconvenience. The clinical evidence-based analysis has found that oral supplementation is as effective as intramuscular injections.

OBJECTIVES

This economic analysis aimed to estimate the cost savings of switching from intramuscular injections to high-dose oral supplements for patients aged 18 years and older with confirmed vitamin B12 deficiency.

DATA SOURCES

Population-based administrative databases for Ontario were used to identify patients receiving vitamin B12 intramuscular injections in any fiscal year between 2006 and 2011. The Ontario Drug Benefit (ODB) database was used to identify patients who were prescribed vitamin B12 injections, and the Ontario Health Insurance Plan database was used to identify all physician claims for intramuscular injections as well as laboratory tests assessing vitamin B12 levels. The Registered Physicians Database was used to identify the type of physician; the analysis was restricted to family physicians and internists.

REVIEW METHODS

Two cohorts of patients were identified. For cohort 1, the ODB database was used to identify patients who were prescribed vitamin B12 injections. Those covered under the ODB are 65 years of age or older and are economically deprived. A second cohort was created to capture those 18 to 64 years of age receiving injections. Cohort 2 consisted of patients (not in cohort 1) who received 6 or more intramuscular injections within 1 year and had a laboratory test 2 months before the intramuscular injection claim. Physician experts were consulted to estimate the resources and costs of converting patients to oral supplements. The Ministry of Health and Long-Term Care perspective was taken, and all costs are expressed in 2013 Canadian dollars.

RESULTS

The budget impact analysis demonstrated costs of $2.8 million to the Ministry of Health and Long-Term Care in the first year of conversion; however, in subsequent years there are savings of $4.2 million per year. The cumulative 5-year budget impact demonstrates savings of $14.2 million to the health care system.

LIMITATIONS

This analysis represents the cost of conversion for those currently receiving intramuscular injections. There are no conversion costs for those who are prescribed oral supplements as an initial therapy, and so the savings could be even greater than reported. As well, an underlying assumption of this analysis is that patients will comply with oral supplementation.

CONCLUSIONS

Over 5 years, there are savings of $14.2 million to the health care system from switching to vitamin B12 oral supplements.

PLAIN LANGUAGE SUMMARY

Vitamin B12 deficiency has long been thought to be associated with dementia and other neurocognitive disorders. In a separate report, Health Quality Ontario (HQO) reviewed the published research on this issue and found only weak evidence that vitamin B12 deficiency is associated with the onset of dementia. That review also found moderate evidence that treatment with vitamin B12 does not improve dementia and that oral supplements are as effective as injections of vitamin B12. In 2010, more than 2.9 million serum vitamin B12 tests were performed in Ontario at a cost of $40 million. Each year, approximately 110,000 residents receive vitamin B12 injections to boost their levels of vitamin B12. HQO commissioned an economic analysis to estimate the cost savings of switching from vitamin B12 injections to high-dose oral supplements for patients aged 18 years and older with confirmed B12 deficiency. This study concluded that the Ontario health care system could save $14.5 million in 5 years by switching to oral supplements, assuming that patients took the oral supplements as required.

Full text, graphs, charts and 6 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3874775/

“Italian children and adolescents who were not receiving vitamin D supplementation had high prevalence of hypovitaminosis D. Careful identification of factors affecting vitamin D status is advisable to promptly start vitamin D supplementation in children and adolescents.”

European Journal Of Pediatrics • December 2013

Vitamin D status and predictors of hypovitaminosis D in Italian children and adolescents: a cross-sectional study

Vierucci F, Del Pistoia M, Fanos M, Gori M,
Carlone G, Erba P, Massimetti G, Federico G, Saggese G.

Abstract

Hypovitaminosis D affects children and adolescents all around the world. Italian data on vitamin D status and risk factors for hypovitaminosis D during pediatric age are lacking. Six hundred fifty-two children and adolescents (range 2.0-21.0 years) living in the northwestern area of Tuscany were recruited at the Department of Pediatrics, University Hospital Pisa. None of them had received vitamin D supplementation in the previous 12 months. 25-hydroxyvitamin D (25-OH-D) and parathyroid hormone (PTH) levels were analyzed in all subjects. Severe vitamin D deficiency was defined as serum levels of 25-OH-D<25.0 nmol/L (10.0 ng/mL) and vitamin D deficiency a<50.0 nmol/L (20.0 ng/mL). Serum 25-OH-D levels of 50.0-74.9 nmol/L (20.0-29.9 ng/mL) indicated vitamin D insufficiency, whereas 25-OH-D levels ≥ 75.0 nmol/L (30.0 ng/mL) were considered sufficient. Hypovitaminosis D was defined as 25-OH-D levels<75.0 nmol/L (30.0 ng/mL). The median serum 25-OH-D level was 51.8 nmol/L, range 6.7-174.7 (20.7 ng/mL, range 2.7-70.0), with a prevalence of vitamin D deficiency, insufficiency, and sufficiency of 45.9, 33.6, and 20.5 %, respectively. The prevalence of severe vitamin D deficiency was 9.5 %. Adolescents had lower median 25-OH-D levels (49.8 nmol/L, range 8.1-174.7; 20.0 ng/mL, range 3.2-70.0) than children (55.6 nmol/L, range 6.8-154.6; 22.3 ng/mL, range 2.7-61.9, p=0.006). Non-white individuals (n=37) had median serum 25-OH-D levels in the range of deficiency (28.2 nmol/L, range 8.1-86.2; 11.3 ng/mL, range 3.2-34.5), with 36/37 having hypovitaminosis D. Logistic regression showed significant increased risk of hypovitaminosis D in the following: blood samples taken in winter (odds ratio (OR) 27.20), spring (OR 26.44), and fall (OR 8.27) compared to summer; overweight (OR 5.02) and obese (OR 5.36) subjects compared to individuals with normal BMI; low sun exposure (OR 8.64) compared to good exposure, and regular use of sunscreens (OR 7.06) compared to non-regular use. Gender and place of residence were not associated with vitamin D status. The 25-OH-D levels were inversely related to the PTH levels (r=-0.395, p<0.0001). Sixty-three out of the 652 (9.7 %) subjects showed secondary hyperparathyroidism.

CONCLUSION

Italian children and adolescents who were not receiving vitamin D supplementation had high prevalence of hypovitaminosis D. Careful identification of factors affecting vitamin D status is advisable to promptly start vitamin D supplementation in children and adolescents.

http://www.ncbi.nlm.nih.gov/pubmed/23959324

“High prevalence of 25(OH)D insufficiency/deficiency was found in patients with systemic lupus erythematosus (57.7%), with statistically significant difference as compared with the comparison group.”

Reumatology • January 2012

25-Hydroxyivitamin D3 levels in patients with systemic lupus erythematosus and its association with clinical parameters and laboratory tests

Author information
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Abstract

INTRODUCTION
The immunoregulatory role of vitamin D has been the object of a growing number of studies in patients with systemic lupus erythematosus (SLE).

OBJECTIVES
To determine the serum levels of 25-hydroxyvitamin D3 [25(OH) D] in patients with SLE, and to assess the association of 25(OH)D insufficiency/deficiency with clinical parameters and laboratory tests.

METHODS
Cross-sectional, prospective study performed at the SLE Clinic, Department of Rheumatology, Hospital das Clínicas, Universidade Federal de Pernambuco with convenience sampling, including 78 patients with SLE and 64 volunteers (comparison group), matched by gender and age.

RESULTS
Insufficiency/deficiency of 25(OH)D was found in 45 (57.7%) patients with SLE and 25 (39%) individuals in the comparison group. The mean serum levels of 25(OH)D were 29.3 ng/mL (6.1-55.2 ng/mL) in patients with SLE and 33.12 ng/mL (15.9-63.8 ng/mL) in the comparison group, and this difference was statistically significant (P = 0.041). No statistically significant difference was observed between the mean ages of both groups. No statistically significant association was observed between 25(OH)D insufficiency/deficiency and the following: time to diagnosis; disease activity (SLEDAI > 6); fatigue; use of corticosteroids and antimalarials; and anti-DNA.

CONCLUSIONS
High prevalence of 25(OH)D insufficiency/deficiency was found in patients with SLE (57.7%), with statistically significant difference as compared with the comparison group. No association of vitamin D insufficiency/deficiency was observed with the clinical variables and laboratory tests studied. The authors emphasize the importance of determining 25(OH)D serum levels in all patients with SLE, regardless of where they live and time to disease diagnosis.

Full text, graphs, charts and 33 references

http://www.scielo.br/pdf/rbr/v52n1/en_v52n1a07.pdf

Mental Health And Family Medicine • January 2012

Postpartum depressive symptoms: the B-vitamin link

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Abstract

“This study examined longitudinal relationships between maternal red-cell folate status and dietary intakes of vitamins B(6), B(12) and folate before and during pregnancy and subsequent postpartum depressive symptoms.Study design and setting Within a cohort study of women aged 20-34 years (the Southampton Women’s Survey) dietary data were obtained before pregnancy and at 11 and 34 weeks’ gestation. Red-cell folate was measured before pregnancy and at 11 weeks’ gestation. We derived relative risks of postpartum depressive symptoms using an Edinburgh Postnatal Depression Scale (EPDS) score of ≥ 13 administered from 6 months to 1 year postpartum.Results No significant differences were found between those with postpartum depressive symptoms (n = 905) and those without (n = 1951) in relation to red-cell folate concentration or dietary intake of folate, vitamin B(12) and vitamin B(6), before or during pregnancy. A prior history of mental illness (relative risk (RR) 1.83; 95% confidence interval (CI) 1.53-2.19) was associated with postpartum depressive symptoms, and women who breastfed until 6 months were less likely to experience postpartum depressive symptoms (RR 0.68; 95% CI 0.55-0.84). Conclusion: This study suggests that folate status and dietary folate, B(6) and B(12) intakes before and during pregnancy are not associated with postpartum depressive symptoms. A history of mental illness, however, was a strong risk factor.”

http://www.ncbi.nlm.nih.gov/pubmed/23277793

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Determination of vitamin B12 in infant formula and adult nutritionals by surface plasmon resonance: First Action 2011.16 (test kit method)

Author information

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Abstract

At the "Standards Development and International Harmonization: AOAC INTERNATIONAL Mid-Year Meeting" on June 29, 2011, an Expert Review Panel (ERP) agreed to further examine AOAC Official Method 2011.01, "Determination of Vitamin B12 by Surface Plasmon Resonance," for use with infant formula and adult nutritionals. The original collaborative study was conducted using the Biacore Q biosensor instrument and the Biacore Q Qflex Kit Vitamin B12 PI. Samples included in the study were infant formula, cereals, premixes, vitamin tablets, dietary supplements, and baby food. Eleven laboratories participated in the collaborative study. The results demonstrated a repeatability RSD (RSDr) of 1.59-27.8 and HorRat values for reproducibility of 0.34-1.89 in samples with levels ranging from ppm to ppb. The assay studied is a label-free protein binding-based assay that uses the principle of surface plasmon resonance to measure the interaction between vitamin B12 and a specific binding protein by passing a portion of the prepared sample extract combined with binding protein solution across a functionalized sensor chip. The response from the functionalized sensor chip is given as free-binding protein, as the mixture binds to the prepared surface of the chip. The ready-to-use Qflex Kit Vitamin B12 PI provides the reagents and accessories necessary to perform this assay. AOAC Method 2011.01 was approved by the AOAC Method Committee on Food Nutrition for Official First Action status, applicable to a wide range of food products, dietary supplements, and multivitamin premixes. After evaluation of the validation data available, an ERP agreed in June 2011 that the method meets standard method performance requirements, as articulated by the Stakeholder Panel on Infant Formula and Adult Nutritionals. The ERP granted the method First Action status, applicable to infant formula and adult/pediatric nutritional formula.

http://www.ncbi.nlm.nih.gov/pubmed/22649915

Chapter 5 • Vitamin B12

Role of vitamin B12 in human metabolic processes

Although the nutritional literature still uses the term vitamin B12, a more specific name for vitamin B12 is cobalamin. Vitamin B12 is the largest of the B complex vitamins, with a molecular weight of over 1000. It consists of a corrin ring made up of four pyrroles with cobalt at the center of the ring (1, 2).

There are several vitamin B12-dependent enzymes in bacteria and algae, but no species of plants have the enzymes necessary for vitamin B12 synthesis. This fact has significant implications for the dietary sources and availability of vitamin B12. In mammalian cells there are only two vitamin B12-dependent enzymes (3). One of these enzymes, methionine synthase, uses the chemical form of the vitamin which has a methyl group attached to the cobalt and is called methylcobalamin (see Figure 7 in Chapter 4.). The other enzyme, methylmalonyl CoA mutase, uses vitamin B12 with a 5'-adeoxyadenosyl moiety attached to the cobalt and is called 5'-deoxyaldenosylcobalamin, or coenzyme B12. In nature there are two other forms of vitamin B12: hydroxycobalamin and aquacobalamin, where hydroxyl and water groups, respectively, are attached to the cobalt. The synthetic form of vitamin B12 found in supplements and fortified foods is cyanocobalamin, which has cyanide attached to the cobalt. These three forms of B12 are enzymatically activated to the methyl- or deoxyadenosylcobalamins in all mammalian cells.

Dietary sources and availability

Most microorganisms, including bacteria and algae, synthesise vitamin B12, and they constitute the only source of the vitamin (4). The vitamin B12 synthesised in microorganisms enters the human food chain through incorporation into food of animal origin. In many animals gastrointestinal fermentation supports the growth of these vitamin B12-synthesising microorganisms, and subsequently the vitamin is absorbed and incorporated into the animal tissues. This is particularly true for the liver, where vitamin B12 is stored in large concentrations. Products from these herbivorous animals, such as milk, meat, and eggs, constitute important dietary sources of the vitamin unless the animal is subsisting in one of the many regions known to be geochemically deficient in cobalt (5). Milk from cows and humans contains binders with very high affinity for vitamin B12, whether they hinder or promote intestinal absorption is not entirely clear. Omnivores and carnivores, including humans, derive dietary vitamin B12 from animal tissues or products (i.e., milk, butter, cheese, eggs, meat, poultry, etc.). It appears that no significant amount of the required vitamin B12 by humans is derived from microflora, although vegetable fermentation preparations have also been reported as being possible sources of vitamin B12 (6).

Absorption

The absorption of vitamin B12 in humans is complex (1, 2). Vitamin B12 in food is bound to proteins and is released from the proteins by the action of a high concentration of hydrochloric acid present in the stomach. This process results in the free form of the vitamin, which is immediately bound to a mixture of glycoproteins secreted by the stomach and salivary glands. These glycoproteins, called R-binders (or haptocorrins), protect vitamin B12 from chemical denaturation in the stomach. The stomach's parietal cells, which secrete hydrochloric acid, also secrete a glycoprotein called intrinsic factor. Intrinsic factor binds vitamin B12 and ultimately enables its active absorption. Although the formation of the vitamin B12 - intrinsic factor complex was initially thought to happen in the stomach, it is now clear that this is not the case. At an acidic pH the affinity of the intrinsic factor for vitamin B12 is low whereas its affinity for the R-binders is high. When the contents of the stomach enter the duodenum, the R-binders become partly digested by the pancreatic proteases, which causes them to release their vitamin B12. Because the pH in the duodenum is more neutral than that in the stomach, the intrinsic factor has a high binding affinity to vitamin B12, and it quickly binds the vitamin as it is released from the R-binders. The vitamin B12-intrinsic factor complex then proceeds to the lower end of the small intestine, where it is absorbed by phagocytosis by specific ileal receptors (1, 2).

Populations at risk for and consequences of vitamin B12 deficiency • Vegetarians

Because plants do not synthesise vitamin B12, individuals who consume diets completely free of animal products (vegan diets) are at risk of vitamin B12 deficiency. This is not true of lacto-ovo-vegetarians, who consume the vitamin in eggs, milk, and other dairy products.

Pernicious anaemia

Malabsorption of vitamin B12 can occur at several points during digestion (1, 4). By far the most important condition resulting in vitamin B12 malabsorption is the auto-immune disease called pernicious anaemia (PA). In most cases of PA, antibodies are produced against the parietal cells causing them to atrophy, lose their ability to produce intrinsic factor, and secrete hydrochloric acid. In some forms of PA the parietal cells remain intact but auto-antiobodies are produced against the intrinsic factor itself and attach to it, thus preventing it from binding vitamin B12. In another less common form of PA, the antibodies allow vitamin B12 to bind to the intrinsic factor but prevent the absorption of the intrinsic factor-vitamin B12 complex by the ileal receptors. As is the case with most auto-immune diseases, the incidence of PA

increases markedly with age. In most ethnic groups it is virtually unknown to occur before the age of 50, with a progressive rise in incidence thereafter (4). However, African American populations are known to have an earlier age of presentation (4). In addition to causing malabsorption of dietary vitamin B12, PA also results in an inability to reabsorb the vitamin B12 which is secreted in the bile. Biliary secretion of vitamin B12 is estimated to be between 0.3 and 0.5 µg/day. Interruption of this so-called enterohepatic circulation of vitamin B12 causes the body to go into a significant negative balance for the vitamin. Although the body typically has sufficient vitamin B12 stores to last 3-5 years, once PA has been established the lack of absorption of new vitamin B12 is compounded by the loss of the vitamin because of negative balance. When the stores have been depleted, the final stages of deficiency are often quite rapid, resulting in death in a period of months if left untreated.

Atrophic gastritis

Historically, PA was considered to be the major cause of vitamin B12 deficiency, but it was a fairly rare condition, perhaps affecting 1 percent to a few percent of elderly populations. More recently it has been suggested that a far more common problem is that of hypochlorhydria associated with atrophic gastritis, where there is a progressive reduction with age of the ability of the parietal cells to secrete hydrochloric acid (7). It is claimed that perhaps up to one-quarter of elderly subjects could have various degrees of hypochlorhydria as a result of atrophic gastritis. It has also been suggested that bacterial overgrowth in the stomach and intestine in individuals suffering from atrophic gastritis may also reduce vitamin B12 absorption. This absence of acid is postulated to prevent the release of protein-bound vitamin B12 contained in food but not to interfere with the absorption of the free vitamin B12 found in fortified foods or supplements. Atrophic gastritis does not prevent the reabsorption of bilary vitamin B12 and therefore does not result in the negative balance seen in individuals with PA. However, it is agreed that with time, a reduction in the amount of vitamin B12 absorbed from the diet will eventually deplete even the usually adequate vitamin B12 stores, resulting in overt deficiency.

When considering recommended nutrient intakes (RNIs) for vitamin B12 for the elderly, it is important to take into account the absorption of vitamin B12 from sources such as fortified foods or supplements as compared with dietary vitamin B12. In the latter instances, it is clear that absorption of intakes of less than 1.5-2.0 µg/day is complete - that is, for intakes of less than 1.5-2.0 µg of free vitamin B12, the intrinsic factor - mediated system absorbs all of that amount. It is probable that this is also true of vitamin B12 in fortified foods, although this has not specifically been examined. However, absorption of food-bound vitamin B12 has been reported to vary from 9 percent to 60 percent depending on the study and the source of the vitamin, which is perhaps related to its incomplete release from food (8). This has led many to estimate absorption as being up to 50 percent to correct for bio-availability of absorption from food.

Vitamin B12 interaction with folate or folic acid

One of the vitamin B12 - dependent enzymes, methionine synthase, functions in one of the two folate cycles (see Chapter 4) - the methylation cycle. This cycle is necessary to maintain availability of the methyl donor S-adenosylmethionine; interruption reduces the wide range of methylated products. One such important methylation is that of myelin basic protein. Reductions in the level of S-adenosylmethionine seen in PA and other causes of vitamin B12 deficiency produce demyelination of the peripheral nerves and the spinal column, called sub-acute combined degeneration (1, 2). This neuropathy is one of the main presenting conditions in PA. The other principal presenting condition in PA is a megaloblastic anaemia morphologically identical to that seen in folate deficiency. Disruption of the methylation cycle should cause a lack of DNA biosynthesis and anaemia.

The methyl trap hypothesis is based on the fact that once the cofactor 5,10-methylenetetrahydrofolate is reduced by its reductase to form 5-methyltetrahydrofolate, the reverse reaction cannot occur. This suggests that the only way for the methyltetrahydrofolate to be recycled to tetrahydrofolate, and thus to participate in DNA biosynthesis and cell division, is through the vitamin B12 - dependent enzyme methionine synthase. When the activity of this synthase is compromised, as it would be in PA, the cellular folate will become progressively trapped as 5-methyltetrahydrofolate. This will result in a cellular pseudo folate deficiency where despite adequate amounts of folate an anaemia will develop that is identical to that seen in true folate deficiency. Clinical symptoms of PA, therefore, include neuropathy, anaemia, or both. Treatment with vitamin B12, if given intramuscularly, will reactivate methionine synthase, allowing myelination to restart. The trapped folate will be released and DNA synthesis and generation of red cells will cure the anaemia. Treatment with high concentrations of folic acid will treat the anaemia but not the neuropathy of PA. It should be stressed that the so-called masking of the anaemia of PA is generally agreed not to occur at concentrations of folate found in food or at intakes of the synthetic form of folic acid found at usual RNI levels of 200 or 400 µg/day (1). However, there is some evidence that amounts less than 400 µg may cause a haematologic response and thus potentially treat the anaemia (9). The masking of the anaemia definitely occurs at high concentrations of folic acid (>1000 µg/day). This becomes a concern when considering fortification with synthetic folic acid of a dietary staple such as flour (see Chapter 4).

In humans the vitamin B12 - dependent enzyme methylmalonyl coenzyme A (CoA) mutase functions in the metabolism of propionate and certain of the amino acids, converting them into succinyl CoA, and in their subsequent metabolism via the citric acid cycle. It is clear that in vitamin B12 deficiency the activity of the mutase is compromised, resulting in high plasma or urine concentrations of methylmalonic acid (MMA), a degradation product of methylmalonyl CoA. In adults this mutase does not appear to have any vital function, but it clearly has an important role during embryonic life and in early development. Children deficient in this enzyme, through rare genetic mutations, suffer from mental retardation and other developmental defects.

Assessment of vitamin B12 status

Traditionally it was thought that low vitamin B12 status was accompanied by a low serum or plasma vitamin B12 level (4). Recently this has been challenged by Lindenbaum et al.(10), who suggested that a proportion of people with normal vitamin B12 levels are in fact vitamin B12 deficient. They also suggested that elevation of plasma homo-cysteine and plasma MMA are more sensitive indicators of vitamin B12 status. Although plasma homo-cysteine may also be elevated because of folate or vitamin B6 deficiency, elevation of MMA apparently always occurs with poor vitamin B12 status. There may be other reasons why MMA is elevated, such as renal insufficiency, so the elevation of itself is not diagnostic. Many would feel that low or decreased plasma vitamin B12 levels should be the first indication

of poor status and that this could be confirmed by an elevated MMA if this assay was available.

Evidence on which to base a recommended intake
Recommendations for nutrient intake

The Food and Nutrition Board of the National Academy of Sciences (NAS) Institute of Medicine (8) has recently exhaustively reviewed the evidence of intake, status, and health for all age groups and during pregnancy and lactation. This review has lead to calculations of what they have called an estimated average requirement (EAR). The EAR is defined by NAS as "the daily intake value that is estimated to meet the requirement, as defined by the specific indicator of adequacy, in half of the individuals in a life-stage or gender group" (8). They have estimated the recommended dietary allowances to be this figure plus 2 standard deviations (SDs). Some members of the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) Expert Consultation were involved in the preparation and review of the NAS recommendations and judge them to have been the best estimates based on available scientific literature. The FAO/WHO expert group felt it appropriate to adopt the same approach used by the NAS in deriving the RNIs. Therefore the RNIs suggested in Table 14 [at right] are based on the NAS EARs plus 2 SDs.

Adults

Several lines of evidence point to an adult average requirement of about 2.0 µg/day. The amount of intramuscular vitamin B12 needed to maintain remission in people with PA suggests a requirement of about 1.5 µg/day (10), but they would also be losing 0.3-0.5µg/day through interruption of their enterohepatic circulation, which is not typical. This might suggest a requirement of 0.7-1.0 µg/day. Because vitamin B12 is not completely absorbed from food, an adjustment of 50 percent has to be added giving a range of 1.4-2.0 µg/day (4). Therapeutic response to ingested food vitamin B12 suggests a minimum requirement of something less than 1.0 µg/day (8). Diets containing 1.8 µg/day seemed to maintain adequate status but lower intakes showed some signs of deficiency. (8). Dietary intakes of less than 1.5 µg/day were reported to be inadequate in some subjects (11).

In summary, the average requirement could be said to be 2 µg/day (8). The variability of the requirements for vitamin B12 is accounted for by adding two SDs, that is, 2.4 µg/day as an RNI for adults, including the elderly.

Table 14 is the Estimated average requirement (EAR) and recommended nutrient intake (RNI) for vitamin B12, by age group, adapted from the US National Academy of Sciences (8).

Group	EAR µg/day	RNI µg/day
Infants and children		
0-6 months	0.32	0.4
7-12 months	0.32	0.5
1-3 years	0.7	0.9
4-6 years	1.0	1.2
7-9 years	1.5	1.8
Adolescents, 10-18 years	2.0	2.4
Adults		
19-65 years	2.0	2.4
65+ years	2.0	2.4
Pregnancy	2.2	2.6
Lactation	2.4	2.8

Children

The Food and Nutrition Board of the NAS Institute of Medicine (8) suggested the same intakes for adolescents with progressive reduction of intake for younger groups.

Pregnancy

The previous FAO/WHO (12) Expert Consultation suggested that 0.1-0.2 µg/day of vitamin B12 is transferred to the foetus (13) during the last two trimesters of pregnancy. On the basis of on foetal liver content from post-mortem samples (14, 15, 16), there is further evidence that the foetus accumulates on average 0.1-0.2 µg/day during pregnancies of women with diets which have adequate vitamin B12. It has been reported that children born to vegetarians or other women with a low vitamin B12 intake subsequently develop signs of clinical vitamin B12 deficiency such as neuropathy (17). Therefore, when calculating the EAR for pregnant women, 0.2 µg/day of vitamin B12 is added to the EAR for adults to result in an EAR of 2.2 µg/day and an RNI of 2.6 µg /day during pregnancy.

Lactation

It is estimated that 0.4 µg/day of vitamin B12 is found in the human milk of women with adequate vitamin B12 status (8). Therefore an extra 0.4 µg/day of vitamin B12 is needed during lactation in addition to the normal adult requirement of 2.0 µg/day, giving a total EAR of 2.4 µg/day during lactation and an RNI of 2.8 µg/day.

Infants

As with other nutrients, the principal way to determine requirements of infants is to examine the levels in milk from mothers on adequate diets. There is a wide difference in the vitamin B12 values reported in human milk because of differences in methodology. The previous FAO/WHO report (12) used milk vitamin B12 values of normal women of about 0.4 µg/l. For an average milk production of 0.75 l/day, the vitamin B12 intake by infants would be 0.3 µg/day (18). Other studies have reported ranges of vitamin B12 in human milk to be 0.4-0.8 µg/L (17, 19, 20, 21, 22). Although daily intakes ranging from 0.02 to 0.05 µg/day have been found to prevent deficiency (23, 24), these intakes are totally inadequate for long-term health. An EAR of 0.3-0.6 µg/day would result in an RNI of 0.36-0.72 µg/d. It might be prudent to use the lower figure of 0.4 µg/day for the first 6 months of pregnancy and 0.7 µg/day for last trimester.

Upper limits

The absorption of vitamin B12 mediated by intrinsic factor is limited to 1.5-2.0 µg per meal because of the limited capacity of the receptors. In addition, between 1 percent and 3 percent of any particular oral administration of vitamin B12 is absorbed by passive diffusion. Thus, if 1000 µg vitamin B12 (sometimes used to treat those with PA) is taken orally, the amount absorbed would be 2.0 µg by active absorption plus about 30 µg by passive diffusion. This amount has never been reported to have any side effects (8). Similar large amounts have been used in some preparations of nutritional supplements without apparent ill effects. However, there are no established benefits for such amounts. Such high intakes thus represent no benefit in those without malabsorption and should probably be avoided.

Future research

Because they do not consume any animal products, vegans are at risk of vitamin B12 deficiency. It is generally agreed that in some communities the only source of vitamin B12 is from contamination of food by microorganisms. When vegans move to countries where standards of hygiene are more stringent, there is good evidence that risk of vitamin B12 deficiency increases in adults and, particularly, in children born to and breast-fed by women who are strict vegans.

• As standards of hygiene improve in developing countries, there is a concern that the prevalence of vitamin B12 deficiency might increase. This should be ascertained by estimating plasma vitamin B12 levels, preferably in conjunction with plasma MMA levels in representative adult populations and in infants.

• The contribution which fermented vegetable foods make to vitamin B12 status of vegan communities should be investigated.

• The prevalence of atrophic gastritis should be investigated in developing countries.

Original Text

http://www.fao.org/docrep/004/Y2809E/y2809e0b.htm

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“Systemic lupus erythematosus patients, especially those with leucopenia or renal involvement, are at high risk of vitamin D deficiency and require vitamin D supplementation.”

Lupus • April 2012

Vitamin D status in systemic lupus erythematosus patients and its association with selected clinical and laboratory parameters

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Abstract

OBJECTIVES

To identify relationships between vitamin D serum levels and the presence of autoantibodies directed against vitamin D and levels of interleukin(IL)-17 and IL-23 in patients with systemic lupus erythematosus (SLE).

METHODS

The study included 49 patients with SLE. Serum concentrations of 25(OH)D(3) were measured with electrochemiluminescence immunoassay (ECLIA). Enzyme-linked immunosorbent assays (ELISA) were used to determine antibodies directed against 1,25(OH)(2)D(3) and levels of IL-17 and IL-23 in serum of SLE patients. In evaluation of vitamin D status, the control group consisted of 49 age and gender matched healthy individuals, whereas in assessment of anti-vitamin D antibodies the control group comprised 30 sera from blood donors.

RESULTS

Serum concentration of 25(OH)D(3) in SLE patients during the warm season was 18.47±9.14 ng/ml, which was significantly decreased as compared with that of the control group - 31.27±12.65 ng/ml ($p=0.0005$). During the cold season a trend toward lower concentration of 25(OH)D(3) in SLE patients was revealed; however, it did not reach statistical significance (11.71±7.21 ng/ml vs. 16.01±8.46 ng/ml; $p=0.054$). Results within the recommended range for vitamin D (30-80 ng/ml; 70-200 nmol/l) were observed only in three patients. The 25(OH)D(3) concentration was decreased in SLE patients with renal disease or leucopenia as compared with the levels in patients who did not have either problem ($p=0.006$ and $p=0.047$, respectively). The cold season was found to be a risk factor for vitamin D deficiency (<20 ng/ml) (odds ratio=9.25; $p=0.005$). Autoantibodies directed against 1,25(OH)(2)D(3) were detected in three SLE patients. No significant difference in 25(OH)D(3) serum concentrations was found between SLE patients with and without these autoantibodies. No link was shown between the existence of autoantibodies against 1,25(OH)(2)D(3) and clinical or laboratory findings, including IL-17 and IL-23 levels. However, serum concentrations of IL-23 were lower in patients with vitamin D deficiency ($p=0.037$).

CONCLUSIONS

SLE patients, especially those with leucopenia or renal involvement, are at high risk of vitamin D deficiency and require vitamin D supplementation. Some SLE patient sera contained 1,25(OH)(2)D(3) antibodies, but these antibodies do not appear to affect vitamin D levels.

http://www.ncbi.nlm.nih.gov/pubmed/22065093

“CONCLUSION: This case underlines the importance of adequately controlling maternal vitamin B12 intake during pregnancy by means of supplementation which, in the case of vegan mothers, should be significantly greater than that usually given. Moreover, the supplementation should be continued during lactation in order to avoid the development of signs of deficiency that may be associated with persistent neurological problems in infants. The case also highlights the need to consider vitamin B12 deficiency in infants with severe anemia even if their hematological parameters do not indicatemegaloblastic anemia because the concomitant presence of substantial iron deficiency may modify the characteristics of the anemia.”

BMC Pediatrics • June 2012

Severe vitamin B12 deficiency in an exclusively breastfed 5-month-old Italian infant born to a mother receiving multivitamin supplementation during pregnancy

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Abstract

BACKGROUND
In infants, vitamin B12 deficiency may be due to an inborn error of absorption and metabolism, or nutritional problems.
CASE PRESENTATION
An exclusively breastfed 5-month-old Italian male infant, who was born after a normal full-term pregnancy to a vegan mother who was apparently daily treated with a multivitamin oral preparation during the second and third trimester, was hospitalised because of poor weight gain, feeding difficulties, severe pallor, muscle hypotonia and somnolence. Upon admission, his weight, length and head circumference were below the third percentile, he had an enlarged liver and spleen, and showed a significant delay in developmental milestones and communicative reactions. He had a hemoglobin level of 4.7 g/dL with an MCV of 84.2 fL, a white blood cell count of 4,680/mm3, and a platelet count of 45,000/mm3. His serum vitamin B12 level was 57 pg/mL (normal value 180-500 pg/mL) and serum folate level 12.8 ng/mL (normal value >3 ng/mL). The results of metabolic examinations excluded a cobalamin C disorder, whereas nutritional screening showed a serum iron concentration of 9 µg/dL and serum ferritin of 4 ng/mL. Magnetic resonance imaging of the brain showed mild dilatation of the lateral ventricles with diffuse delayed myelination. The child was diagnosed as having vitamin B12 and iron deficiency due to nutritional inadequacy and was immediately treated with packed red blood cells, intramuscular vitamin B12 injections, and iron supplementation. A few days after the start of therapy, his hemoglobin levels and other hematological parameters rapidly improved, and a clinical improvement was observed within few weeks. There was an increase in his achievement of developmental milestones, but his development was still retarded seven months after the start of therapy.

Full text with 18 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3407531/

Pediatrics • September 2012

Vitamin D deficiency in critically ill children

Author information

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Abstract

OBJECTIVE

Vitamin D influences cardiovascular and immune function. We aimed to establish the prevalence of vitamin D deficiency in critically ill children and identify factors influencing admission 25-hydroxy vitamin D (25(OH)D) levels. We hypothesized that levels would be lower with increased illness severity and in children with serious infections.

METHODS

Participants were 511 severely or critically ill children admitted to the PICU from November 2009 to November 2010. Blood was collected near PICU admission and analyzed for 25(OH)D concentration by using Diasorin radioimmunoassay.

RESULTS

We enrolled 511 of 818 (62.5%) eligible children. The median 25(OH)D level was 22.5 ng/mL; 40.1% were 25(OH)D deficient (level <20 ng/mL). In multivariate analysis, age and race were associated with 25(OH)D deficiency; summer season, vitamin D supplementation, and formula intake were protective; 25(OH)D levels were not lower in the 238 children (46.6%) admitted with a life-threatening infection, unless they had septic shock (n = 51, 10.0%) (median 25(OH)D level 19.2 ng/mL; P = .0008). After adjusting for factors associated with deficiency, lower levels were associated with higher admission day illness severity (odds ratio 1.19 for a 1-quartile increase in Pediatric Risk of Mortality III score per 5 ng/mL decrease in 25(OH)D, 95% confidence interval 1.10-1.28; P < .0001).

CONCLUSIONS

We found a high rate of vitamin D deficiency in critically ill children. Given the roles of vitamin D in bone development and immunity, we recommend screening of those critically ill children with risk factors for vitamin D deficiency and implementation of effective repletion strategies.

Full text, graphs, charts and 49 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074622/

"We found a high rate of vitamin D deficiency in critically ill children.

Given the roles of vitamin D in bone development and immunity, we recommend screening of those critically ill children with risk factors for vitamin D deficiency and implementation of effective repletion strategies."

“This study supports the presence of an association between high 25(OH)D levels during the years preceding disease onset and a **decreased risk** of multiple sclerosis ... Decreasing 25(OH)D levels in the population may contribute to explain the increasing multiple sclerosis incidence that is suggested from epidemiologic studies.”

Neurology • November 2012

Vitamin D as a protective factor in multiple sclerosis

Salzer J1, Hallmans G, Nyström M, Stenlund H, Wadell G, Sundström P.

Abstract

OBJECTIVE

To examine the association between 25-hydroxyvitamin D (25[OH]D) levels and the risk of multiple sclerosis (MS) in blood samples collected prospectively and during gestation.

METHODS

In this nested case-control study, 2 population-based biobanks with 291,500 samples from 164,000 persons collected since 1975 in the northern half of Sweden were used. We identified prospectively collected blood samples from MS cases (n = 192, controls matched 2:1) and gestational samples from pregnant mothers where the offspring had later developed MS (n = 37, control mothers matched 5:1). 25(OH)D levels were measured using an ELISA, and the risk of MS was analyzed using matched logistic regression.

RESULTS

Levels of 25(OH)D ≥75 (vs <75) nmol/L in prospectively collected blood samples were associated with a decreased risk of MS (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.16-0.98). No decrease in MS risk was found in the offspring exposed to gestational 25(OH)D levels ≥75 (vs <75) nmol/L (OR 1.8, 95% CI 0.53-5.8). The prevalence of 25(OH)D levels ≥75 nmol/L in female controls decreased gradually during 1976-2005 (p trend = 0.005).

CONCLUSION

This study supports the presence of an association between high 25(OH)D levels during the years preceding disease onset and a decreased risk of MS. In the very limited material with samples drawn in early pregnancy, where month-of-birth effects were controlled for, we found no association between gestational 25(OH)D levels and MS risk in the offspring. Decreasing 25(OH)D levels in the population may contribute to explain the increasing MS incidence that is suggested from epidemiologic studies.

http://www.ncbi.nlm.nih.gov/pubmed/23170011

Nutricion Hospitalaria • March 2011

Importance of a balanced omega 6/omega 3 ratio for the maintenance of health: nutritional recommendations

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Abstract

“The modification of dietary patterns has led to a change in fatty acid consumption, with an increase in the consumption of Ω [omega]-6 fatty acids and a marked reduction in the consumption of Ω-3 fatty acids. This in turn has given rise to an imbalance in the Ω-6/Ω-3 ratio, which is now very different from the original 1:1 ratio of humans in the past. Given the involvement of -6 and Ω-3 essential fatty acids in disease processes, the present article examines changes in dietary patterns that have led to the present reduction in the consumption of Ω-3 essential fatty acids, and to study the importance of the Ω-6/Ω-3 balance in maintaining good health. In addition, an assessment is made of the established recommendations for preventing a poor intake of Ω-3 essential fatty acids, and the possible options for compensating the lack of these fatty acids in the diet.”

http://www.ncbi.nlm.nih.gov/pubmed/21666970

Nutrition Reviews • April 2011

Can multi-micronutrient food fortification improve the micronutrient status, growth, health, and cognition of schoolchildren? A systematic review

Author information

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Abstract

“Micronutrient deficiencies compromise the health and development of many school-age children worldwide. Previous research suggests that micronutrient interventions might benefit the health and development of school-age children and that multiple micronutrients might be more effective than single micronutrients. Fortification of food is a practical way to provide extra micronutrients to children. Earlier reviews of (multiple) micronutrient interventions in school-age children did not distinguish between supplementation or fortification studies. The present review includes studies that tested the impact of multiple micronutrients provided via fortification on the micronutrient status, growth, health, and cognitive development of schoolchildren. Twelve eligible studies were identified. Eleven of them tested the effects of multiple micronutrients provided via fortified food compared to unfortified food. One study compared fortification with multiple micronutrients to fortification with iodine alone. Multi-micronutrient food fortification consistently improved micronutrient status and reduced anemia prevalence. Some studies reported positive effects on morbidity, growth, and cognitive outcomes, but the overall effects on these outcomes were equivocal.”

http://www.ncbi.nlm.nih.gov/pubmed/21457264

“The latest generation of smartphones are increasingly viewed as handheld computers rather than as phones, due to their powerful on-board computing capability, capacious memories, large screens and open operating systems that encourage application development. This paper provides a brief state-of-the-art overview of health and healthcare smartphone apps (applications) on the market today, including emerging trends and market uptake.”

Biomedical Engineering Online • April 2011

How smartphones are changing the face of mobile and participatory healthcare: an overview, with example from eCAALYX

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Abstract

The latest generation of smartphones are increasingly viewed as handheld computers rather than as phones, due to their powerful on-board computing capability, capacious memories, large screens and open operating systems that encourage application development. This paper provides a brief state-of-the-art overview of health and healthcare smartphone apps (applications) on the market today, including emerging trends and market uptake. Platforms available today include Android, Apple iOS, RIM BlackBerry, Symbian, and Windows (Windows Mobile 6.x and the emerging Windows Phone 7 platform). The paper covers apps targeting both laypersons/patients and healthcare professionals in various scenarios, e.g., health, fitness and lifestyle education and management apps; ambient assisted living apps; continuing professional education tools; and apps for public health surveillance. Among the surveyed apps are those assisting in chronic disease management, whether as standalone apps or part of a BAN (Body Area Network) and remote server configuration. We describe in detail the development of a smartphone app within eCAALYX (Enhanced Complete Ambient Assisted Living Experiment, 2009-2012), an EU-funded project for older people with multiple chronic conditions. The eCAALYX Android smartphone app receives input from a BAN (a patient-wearable smart garment with wireless health sensors) and the GPS (Global Positioning System) location sensor in the smartphone, and communicates over the Internet with a remote server accessible by healthcare professionals who are in charge of the remote monitoring and management of the older patient with multiple chronic conditions. Finally, we briefly discuss barriers to adoption of health and healthcare smartphone apps (e.g., cost, network bandwidth and battery power efficiency, usability, privacy issues, etc.), as well as some workarounds to mitigate those barriers.

Full text, graphs, charts and 67 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3080339/

Vitamins And Hormones • July 2011

Vitamin D deficiency and connective tissue disease

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Abstract

“Recently, the evidence linking vitamin D status as a potential environmental factor affecting autoimmune disease prevalence continues to accumulate. Beyond that the traditional known metabolic activities, vitamin D has been shown to modulate the immune system and has anti-inflammatory properties. The immune-regulatory role of vitamin D affects both the innate and adaptive immune responses contributing to the immune-tolerance of self-structures. Vitamin D deficiency skews the immunologic response towards loss of tolerance. Serum levels of vitamin D have been found to be significantly lower in several autoimmune or immune-mediated diseases than in the healthy population. Experimental animal models and clinical studies show that 1,25-dihydroxyvitamin D3 or vitamin D receptor (VDR) agonists can either prevent or suppress symptoms of type 1 diabetes, experimental autoimmune encephalomyelitis, rheumatoid arthritis, systemic lupus erthyematosus and inflammatory bowel disease. The heading aims at reviewing the complex immune-regulatory role of vitamin D from the cellular and humoral level through animal models of autoimmune rheumatic diseases and representing the known contribution of vitamin D in the pathogenesis of connective tissue diseases. Increased vitamin D intakes might reduce the incidence and severity of autoimmune disorders besides reducing the rate of osteoporotic bone fracture.”

http://www.ncbi.nlm.nih.gov/pubmed/21419275

“Our findings suggest that a higher sodium-potassium ratio is associated with significantly increased risk of cardiovascular diseases and all-cause mortality, and higher sodium intake is associated with increased total mortality in the general US population.”

Archives In Internal Medicine • July 2011

Sodium and potassium intake and mortality among US adults: prospective data from the Third National Health and Nutrition Examination Survey

Author information

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Abstract

BACKGROUND

Several epidemiologic studies suggested that higher sodium and lower potassium intakes were associated with increased risk of cardiovascular diseases (CVD). Few studies have examined joint effects of dietary sodium and potassium intake on risk of mortality.

METHODS

To investigate estimated usual intakes of sodium and potassium as well as their ratio in relation to risk of all-cause and CVD mortality, the Third National Health and Nutrition Examination Survey Linked Mortality File (1988-2006), a prospective cohort study of a nationally representative sample of 12,267 US adults, studied all-cause, cardiovascular, and ischemic heart (IHD) diseases mortality.

RESULTS

During a mean follow-up period of 14.8 years, we documented a total of 2270 deaths, including 825 CVD deaths and 443 IHD deaths. After multivariable adjustment, higher sodium intake was associated with increased all-cause mortality (hazard ratio [HR], 1.20; 95% confidence interval [CI], 1.03-1.41 per 1000 mg/d), whereas higher potassium intake was associated with lower mortality risk (HR, 0.80; 95% CI, 0.67-0.94 per 1000 mg/d). For sodium-potassium ratio, the adjusted HRs comparing the highest quartile with the lowest quartile were HR, 1.46 (95% CI, 1.27-1.67) for all-cause mortality; HR, 1.46 (95% CI, 1.11-1.92) for CVD mortality; and HR, 2.15 (95% CI, 1.48-3.12) for IHD mortality. These findings did not differ significantly by sex, race/ethnicity, body mass index, hypertension status, education levels, or physical activity.

CONCLUSION

Our findings suggest that a higher sodium-potassium ratio is associated with significantly increased risk of CVD and all-cause mortality, and higher sodium intake is associated with increased total mortality in the general US population.

http://www.ncbi.nlm.nih.gov/pubmed/21747015

“Vitamin D deficiency is widespread and has been associated with many chronic diseases, including autoimmune disorders. A study was undertaken to explore the impact of low vitamin D levels on autoantibody production in healthy individuals, as well as B cell hyperactivity and interferon ß [beta] activity in patients with systemic lupus erythematosus.”

Annals Of Rheumatic Diseases • September 2011

Vitamin D deficiency is associated with an increased autoimmune response in healthy individuals and in patients with systemic lupus erythematosus

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Abstract

OBJECTIVES

Vitamin D deficiency is widespread and has been associated with many chronic diseases, including autoimmune disorders. A study was undertaken to explore the impact of low vitamin D levels on autoantibody production in healthy individuals, as well as B cell hyperactivity and interferon ß (IFNß) activity in patients with systemic lupus erythematosus (SLE).

METHODS

Serum samples from 32 European American female patients with SLE and 32 matched controls were tested for 25-hydroxyvitamin D (25(OH)D) levels, lupus-associated autoantibodies and serum IFNß activity. Isolated peripheral blood mononuclear cells were tested for intracellular phospho-ERK 1/2 as a measure of B cell activation status.

RESULTS

Vitamin D deficiency (25(OH)D <20 ng/ml) was significantly more frequent among patients with SLE (n=32, 69%) and antinuclear antibody (ANA)-positive controls (n=14, 71%) compared with ANA-negative controls (n=18, 22%) (OR 7.7, 95% CI 2.0 to 29.4, p=0.003 and OR 8.8, 95% CI 1.8 to 43.6, p=0.011, respectively). Patients with high B cell activation had lower mean (SD) 25(OH)D levels than patients with low B cell activation (17.2 (5.1) vs 24.2 (3.9) ng/ml; p=0.009). Patients with vitamin D deficiency also had higher mean (SD) serum IFNß activity than patients without vitamin D deficiency (3.5 (6.6) vs 0.3 (0.3); p=0.02).

CONCLUSIONS

The observation that ANA-positive healthy controls are significantly more likely to be deficient in vitamin D than ANA-negative healthy controls, together with the finding that vitamin D deficiency is associated with certain immune abnormalities in SLE, suggests that vitamin D plays an important role in autoantibody production and SLE pathogenesis.

Full text, graphs, charts and 36 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149865/pdf/nihms307669.pdf

Clinical And Experimental Rheumatology • November 2011

Vitamin D levels and potential impact in systemic sclerosis

Author information

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Abstract

“Vitamin D is essential not only for calcium and bone metabolism, but it also may exert other biological activities, including immunomodulation through the expression of vitamin D receptor in antigen-presenting cells and activated T cells. Evidence from animal models and human prospective studies of rheumatoid arthritis, multiple sclerosis, type I diabetes, and systemic lupus erythematosus, indeed suggested an important role for vitamin D as a modifiable environmental factor in autoimmune diseases.”

In systemic sclerosis (SSc), this role has not been completely dissected, although recent studies clearly evidenced a high prevalence of vitamin D deficiency. Moreover, some degree of association between vitamin D deficiency and disease activity or phenotype characteristics has also been observed. Vitamin D deficiency in SSc may be related to several factors: insufficient sun exposure due to disability and skin fibrosis, insufficient intake because of gut involvement and malabsorption. Although it is advisable to regularly check vitamin D status in these patients, there is no consensus about which vitamin D supplementation regimen might be sufficient to modulate immunological homeostasis, and possibly reduce disease activity or severity, thus further prospective studies are needed. Moreover, novel vitamin D analogues with more pronounced immune modulatory effect and lower activity on calcium metabolism are in the pipeline, and might represent a great innovative opportunity for the treatment of vitamin D deficiency in such autoimmune disorders.

http://www.ncbi.nlm.nih.gov/pubmed/22011638

Bone • February 2010

Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly

Author information

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Abstract

Bone mass is a key determinant of fracture risk. Maximizing bone mineral mass during childhood and adolescence may contribute to fracture risk reduction during adolescence and possibly in the elderly. Although more than 60% of the variance of peak bone mass (PBM), the amount of bone present in the skeleton at the end of its maturation process, is genetically determined, the remainder is likely influenced by factors amenable to positive intervention, such as adequate dietary intake of dairy products as a natural source of calcium and proteins, vitamin D, and regular weight-bearing physical activity. Low calcium and vitamin D intakes are associated with negative effects on bone, including suboptimal PBM acquisition.

“As suggested by intervention studies, regular intake of dairy products may have positive and possibly sustained effects on bone mineral mass gain, contributing thereby to fracture risk reduction. Further evidence from intervention studies suggests that weight-bearing physical activities, such as jumping, may contribute to bone mineral mass gain in children. Optimizing PBM acquisition through dietary and physical exercise measures may represent a valuable primary method for the prevention of fractures.”

http://www.ncbi.nlm.nih.gov/pubmed/19840876

Handbook Of Clinical Neurology • March 2010

Chapter 29: historical aspects of the major neurological vitamin deficiency disorders: overview and fat-soluble vitamin A

Author information

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Abstract

The vitamine doctrine: Although diseases resulting from vitamin deficiencies have been known for millennia, such disorders were generally attributed to toxic or infectious causes until the "vitamin doctrine" was developed in the early 20th century. In the late-19th century, a physiologically complete diet was believed to require only sufficient proteins, carbohydrates, fats, inorganic salts, and water. From 1880-1912, Lunin, Pekelharing, and Hopkins found that animals fed purified mixtures of known food components failed to grow or even lost weight and died, unless the diet was supplemented with small amounts of milk, suggesting that "accessory food factors" are required in trace amounts for normal growth. By this time, Funk suggested that deficiencies of trace dietary factors, which he labeled "vitamines" on the mistaken notion that they were "vital amines," were responsible for such diseases as beriberi, scurvy, rickets, and pellagra. Vitamin A deficiency eye disease: Night blindness was recognized by the ancient Egyptians and Greeks, and many authorities from Galen onward advocated liver as a curative. Outbreaks of night blindness were linked to nutritional causes in the 18th and 19th centuries by von Bergen, Schwarz, and others. Corneal ulceration was reported in 1817 by Magendie among vitamin A-deficient dogs fed for several weeks on a diet limited to sugar and water, although he erroneously attributed this to a deficiency of dietary nitrogen (i.e. protein). Subsequently, corneal epithelial defects, often in association with night blindness, were recognized in malnourished individuals subsisting on diets now recognizable as deficient in vitamin A by Budd, Livingstone, von Hubbenet, Bitot, Mori, Ishihari, and others. During World War I, Bloch conducted a controlled clinical trial of different diets among malnourished Danish children with night blindness and keratomalacia and concluded that whole milk, butter, and cod-liver oil contain a fat-soluble substance that protects against xerophthalmia. Early retinal photochemistry: In the 1870s, Boll found that light causes bleaching of the retinal pigment, and suggested that the outer segments of the rods contain a substance that conveys an impression of light to the brain by a photochemical process. Shortly thereafter, Kühne demonstrated that the bleaching process depends upon light, and was reversible if the retinal pigment epithelium was intact. Kühne proposed an "optochemical hypothesis," a prescient concept of photochemical transduction, attributing vision to a photochemical change in visual purple (rhodopsin) with resulting chemical products stimulating the visual cells and thereby conveying a visual image. Vitamin A: In 1913, Ishihara proposed that a "fatty substance" in blood is necessary for synthesis of both rhodopsin and the surface layer of the cornea, and that night blindness and keratomalacia develop when this substance is deficient. That year McCollum and Davis (and almost simultaneously Mendel and Osborne) discovered a fat-soluble accessory food factor (later called "fat-soluble A") distinct from the water-soluble anti-beriberi factor (later called "fat-soluble B"). By 1922 McCollum and colleagues distinguished two vitamins within the fat-soluble fraction, later named vitamins A and D. In 1925 Fridericia and Holm directly linked vitamin A to night blindness in animal experiments using rats, and in 1929 Holm demonstrated the presence of vitamin A in retinal tissue. In the 1930s, Moore, Karrer, Wald, and others established the provitamin role of beta-carotene. Karrer and colleagues isolated beta-carotene (the main dietary precursor of vitamin A) and retinol (vitamin A), and determined their chemical structures. In 1947, Isler and colleagues completed the full chemical synthesis of vitamin A. Modern retinal photochemistry: Beginning in the 1930s, Wald and colleagues greatly elaborated the photochemistry of vision, with the discovery of the visual cycle of vitamin A, demonstration that rhodopsin is decomposed by light into retinal (the aldehyde form of vitamin A) and a protein (opsin), elaboration of the enzymatic conversions of various elements in the rhodopsin system, and discovery that the rhodopsin system is dependent on a photoisomerization of retinal. In 1942, Hecht and colleagues demonstrated that a single photon could trigger excitation in a rod. In 1965, Wald suggested that a large chemical amplification was necessary for this degree of light sensitivity, likely by a cascade of enzymatic reactions. Later studies elaborated this cascade and found that an intermediary in the photoisomerization of retinal interacts with transducin, a G-protein, to activate phosphodiesterases that control cyclic GMP levels, which in turn modulate the release of neurotransmitter from the rod cell. Public health: Although the availability of vitamin A through food fortification and medicinal supplements virtually eliminated ocular vitamin A deficiency from developed countries by the second half of the 20th century, vitamin A deficiency remains a serious problem in developing countries as indicated by global surveys beginning in the 1960s. Millions of children were shown to be vitamin A deficient, with resultant blindness, increased susceptibility to infection, and increased childhood mortality. Beginning in the 1960s, intervention trials showed that vitamin A deficiency disorders could be prevented in developing countries with periodic vitamin A dosing, and in the 1980s and 1990s, large randomized, double-blind, placebo-controlled clinical trials demonstrated the marked efficacy of vitamin A supplementation in reducing childhood mortality.

http://www.ncbi.nlm.nih.gov/pubmed/19892132

Handbook Of Clinical Neurology • April 2010

Chapter 30: historical aspects of the major neurological vitamin deficiency disorders: the water-soluble B vitamins

Author information

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Abstract

This historical review addresses major neurological disorders associated with deficiencies of water-soluble B vitamins: beriberi, Wernicke-Korsakoff syndrome, pellagra, neural tube defects, and subacute combined degeneration of the spinal cord. Beriberi: Beriberi was known for millennia in Asia, but was not described by a European until the 17th century when Brontius in the Dutch East Indies reported the progressive sensorimotor polyneuropathy. The prevalence of beriberi increased greatly in Asia with a change in the milling process for rice in the late 19th century. In the 1880s, Takaki demonstrated the benefits of dietary modification in sailors, and later instituted dietary reforms in the Japanese Navy, which largely eradicated beriberi from the Japanese Navy by 1887. In 1889 Eijkman in Java serendipitously identified dietary factors as a major contributor to "chicken polyneuritis," which he took to be an animal model for beriberi; the polyneuritis could be cured or prevented by feeding the chickens either unpolished rice or rice polishings. By 1901, Grijns, while continuing studies of beriberi in Java, suggested a dietary deficiency explanation for beriberi after systematically eliminating deficiencies of known dietary components and excluding a toxic effect. Wernicke-Korsakoff syndrome: In the late 1870s, Wernicke identified a clinicopathological condition with ophthalmoparesis, nystagmus, ataxia, and encephalopathy, associated with punctate hemorrhages symmetrically arranged in the grey matter around the third and fourth ventricles and the aqueduct of Sylvius. In the late 1880s, Korsakoff described a spectrum of cognitive disorders, including a confabulatory amnestic state following an agitated delirium, occurring in conjunction with peripheral polyneuropathy. Beginning around 1900, investigators recognized the close relationship between Korsakoff's psychosis, delirium tremens, and Wernicke's encephalopathy, but not until several decades later were Wernicke's encephalopathy, Korsakoff's psychosis, and beriberi all linked to the deficiency of a specific dietary factor, i.e. thiamin. Thiamin: Thiamin was crystallized from rice polishings by Jansen and Donath in 1926, and synthesized by Williams and Cline in 1936. In the late 1930s and early 1940s, characteristic pathological changes of Wernicke-Korsakoff syndrome were produced in animal models, the biochemical roles of thiamin in intermediary carbohydrate metabolism were elaborated by Peters and others, and the therapeutic benefits of thiamin for Wernicke-Korsakoff syndrome and beriberi were demonstrated. By the 1950s synthetic forms of the vitamin were produced cheaply, allowing both therapeutic administration and prevention with food enrichment. Pellagra and niacin: Pellagra was unknown prior to the introduction of maize into Europe from the New World. In the 18th century, Casàl and Frapolli described the clinical features of pellagra in Europe, and linked it with poverty and subsistence on nutritionally marginal corn-based diets. In the United States, pellagra became epidemic among poor Southerners in the early 20th century, in part because of economically-driven reliance on monotonous, nutritionally inadequate diets, combined with new manufacturing methods that removed vitamins from processed grain. From 1914-1929, Goldberger completed well-designed epidemiologic investigations, tested theories with human experiments, and utilized an animal model ("black tongue" in dogs) - all strongly supporting a dietary deficiency explanation for pellagra over prevailing toxic and infectious theories. Initial prevention and treatment approaches proved inadequate because of complex social issues linked to poverty, even after Goldberger and colleagues established that dried brewer's yeast could cure or prevent pellagra less expensively than dietary modification. During the depression, the collapse of cotton as an economically viable crop facilitated crop diversification, which contributed to an abrupt decline in pellagra mortality in the early 1930s. In 1937 Elvehjem

isolated the P-P (pellagra preventive) factor, identified it as nicotinic acid (niacin), and demonstrated that nicotinic acid and nicotinic acid amide cure black tongue in dogs. Although clinical trials soon confirmed dramatic therapeutic effects in individual people, therapeutic administration of niacin had relatively little impact on population-level morbidity and mortality. Vitamin fortification of foodstuffs during World War II ultimately eradicated endemic pellagra in the United States. In the 1940s and 1950s, with expanded biochemical knowledge, pellagra was reformulated as a deficiency disease due to inadequate niacin and its amino acid precursor tryptophan. Neural tube defects and folate: Folate deficiency was initially recognized clinically as a macrocytic anemia in the 1920s, and only clearly separated from pernicious anemia by the mid-20th century. When folic acid was isolated and synthesized in the 1940s, it was shown to correct the macrocytic anemia associated with pernicious anemia, while the neurological manifestations progressed. In the 1950s and 1960s, the biochemical role of folates in transferring single carbon units was elucidated. Beginning in the 1960s, folate deficiency was increasingly recognized as the major cause of preventable neural tube defects. In the early 1990s well-designed randomized trials established that folate supplementation could prevent neural tube defects. Trial data, collectively indicating that periconceptual folate administration reduces both the occurrence and recurrence risks of neural tube defects by at least 70%, helped establish governmental recommendations concerning folic acid intake and health policy concerning vitamin fortification of foodstuffs. When dietary modification and supplementation strategies proved inadequate, folic acid food fortification was legally mandated in the US in the late 1990s, which significantly improved population folate status and produced an abrupt decline (20%-27%) in the prevalence of neural tube defects at birth. Recent studies have established genetic predispositions for neural tube defects, including both infant and maternal gene polymorphisms for enzymes involved in folate-dependent homocysteine metabolism, which help explain how the genotype of the mother, the genotype of the unborn child, and environmental factors (e.g. folate intake) can all impact on the risk of neural tube defects. Subacute combined degeneration and B(12) deficiency: Pernicious anemia was recognized clinically in the mid-19th century by Addison, but the most important neurological manifestation - subacute combined degeneration of the spinal cord - was not recognized clinically and linked with pernicious anemia until the end of the 19th century, particularly by Lichtheim, Putnam, and Dana. At the beginning of the 20th century, pernicious anemia and the associated subacute combined degeneration of the spinal cord were considered, by many investigators, to result from infectious or toxic causes. During the first quarter of the 20th century, various therapies were employed, but, with the possible exception of transfusion, were largely ineffective. In the 1920s, Minot and Murphy showed that large quantities of ingested liver could be used to effectively treat pernicious anemia, and specifically could improve or prevent progression of neurological manifestations, and could extend life expectancy beyond 2 years. Beginning in the late 1920s, Castle demonstrated that a substance elaborated by the gastric mucosa ("intrinsic factor") was essential for the absorption of a dietary factor ("extrinsic factor," later shown to be vitamin B(12)) needed to prevent pernicious anemia. Over two decades, from the late 1920s until the late 1940s, increasingly potent liver extracts were manufactured that could be given either intramuscularly or intravenously. In 1947, vitamin B(12) was isolated by Folkers and colleagues, and nearly simultaneously by Smith. Shortly thereafter the therapeutic efficacy of vitamin B(12) on subacute combined degeneration was demonstrated by West and Reisner and others. By 1955, Hodgkin determined the molecular structure of cyanocobalamin using computer-assisted x-ray crystallography, allowing complete chemical synthesis of vitamin B(12) in 1960 by an international consortium. Beginning in the late 1950s, the absorption and biochemistry of vitamin B(12) were elaborated, and several lines of evidence converged to support an autoimmune basis for pernicious anemia.

http://www.ncbi.nlm.nih.gov/pubmed/19892133

Autoimmunity Reviews • May 2010

Vitamin D and autoimmune rheumatologic disorders

Author information

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"Vitamin D levels depend on many variables, including sun exposure, age, ethnicity, body mass index, use of medications and supplements. A much higher oral vitamin D intake than the current guidelines is necessary to maintain adequate circulating 25(OH)D levels in the absence of UVB radiation of the skin. In addition to the traditional known metabolic activities, vitamin D has been shown to modulate the immune system, and its deficiency has been linked to the development of several autoimmune disorders including type 1 diabetes and multiple sclerosis. Experimental use of vitamin D has revealed a novel role in the immunopathogenesis of autoimmune diseases. Disorders such as systemic lupus erythematosus, rheumatoid arthritis, Behçet's, polymyositis/dermatomyositis and systemic scleroderma have all been associated to some extent to vitamin D deficiency. If vitamin D deficiency occurs at a higher rate in patients with autoimmune disorders, then appropriate supplementation may be indicated."

http://www.ncbi.nlm.nih.gov/pubmed/20146942

American Family Physician • June 2010

Evaluation of anemia in children

Author information

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Abstract

“Anemia is defined as a hemoglobin level of less than the 5th percentile for age. Causes vary by age. **Most children with anemia are asymptomatic, and the condition is detected on screening laboratory evaluation.** Screening is recommended only for high-risk children. Anemia is classified as microcytic, normocytic, or macrocytic, based on the mean corpuscular volume. Mild microcytic anemia may be treated presumptively with oral iron therapy in children six to 36 months of age who have risk factors for iron deficiency anemia. If the anemia is severe or is unresponsive to iron therapy, the patient should be evaluated for gastrointestinal blood loss. Other tests used in the evaluation of microcytic anemia include serum iron studies, lead levels, and hemoglobin electrophoresis. Normocytic anemia may be caused by chronic disease, hemolysis, or bone marrow disorders. Workup of normocytic anemia is based on bone marrow function as determined by the reticulocyte count. If the reticulocyte count is elevated, the patient should be evaluated for blood loss or hemolysis. A low reticulocyte count suggests aplasia or a bone marrow disorder. Common tests used in the evaluation of macrocytic anemias include vitamin B12 and folate levels, and thyroid function testing. A peripheral smear can provide additional information in patients with anemia of any morphology.”

http://www.ncbi.nlm.nih.gov/pubmed/20540485

“The results suggest that supplementation with a combination of vitamins E and C reduced lipid peroxidation and strengthened the antioxidant defense system. Hence, there will be beneficial effects on the heart by reducing oxidative stress in cardiovascular disease patients.”

Journal Of Nutrition Science And Vitaminology (Tokyo) • August 2010

Effect of vitamin E and C supplements on antioxidant defense system in cardiovascular disease patients in Zahedan, southeast Iran

Karajibani M1, Hashemi M, Montazerifar F, Dikshit M.

Abstract

Oxidative stress plays an important role in the pathogenesis of cardiovascular disease (CVD). Growing evidence suggest that antioxidant vitamins might reduce the risk of disease outcomes by their ability to scavenge free radicals. The aim of the present study was to evaluate the supplementation of vitamins E and C on oxidant and antioxidant status in CVD patients. We conducted a case-control study with vitamin E (400 IU/d) and vitamin C (500 mg/d) supplementation in 40 CVD patients for 2 mo. Antioxidant (enzymatic and non-enzymatic) and oxidant status were analyzed pre and post supplementation. In the initial stage the activity of both enzymatic and non-enzymatic antioxidants were lower, while the malondialdehyde (MDA) level was elevated ($p<0.0001$). After intervention, a significant increase in superoxide dismutase (SOD) activity (61.7%), glutathione peroxidase (GPx) activity (59.3%), the levels of vitamin E (83.7%), C (145.3%), total antioxidant capacity (TAC) (62.8%) and a significant decrease in MDA (40%) value were observed ($p<0.0001$). There was a significant negative correlation between MDA and TAC. The results suggest that supplementation with a combination of vitamins E and C reduced lipid peroxidation and strengthened the antioxidant defense system. Hence, there will be beneficial effects on the heart by reducing oxidative stress in CVD patients.

http://www.ncbi.nlm.nih.gov/pubmed/21422713

Annals In Neurology • August 2010

Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis

Author information

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Abstract

OBJECTIVE

A protective association between higher vitamin D levels and the onset of multiple sclerosis (MS) has been demonstrated; however, its role in modulating MS clinical course has been little studied. We investigated whether higher levels of serum 25-hydroxyvitamin D (25-OH-D) were associated with a lower risk of relapses in people with MS.

METHODS

We conducted a prospective cohort study of 145 participants with relapsing-remitting MS from 2002 to 2005. Serum 25-OH-D levels were measured biannually, and the hazard of relapse was assessed using survival analysis.

RESULTS

There was an inverse linear relationship between 25-OH-D levels and the hazard of relapse over the subsequent 6 months, with hazard ratio (HR) 0.91 (95% confidence interval [CI]: 0.85-0.97) per 10 nmol/l increase in 25-OH-D level (p = 0.006). When variation due to timing of blood collection was removed by estimating 25-OH-D at the start of each season, this association persisted, with HR 0.90 (95% CI, 0.83-0.98) per 10 nmol/l increase (p = 0.016). Taking into account the biological half-life of 25-OH-D, we estimated 25-OH-D at monthly intervals, resulting in a slightly enhanced association, with HR 0.88 (95% CI, 0.82-0.95) per 10 nmol/l increase (p = 0.001). Adjusting for potential confounders did not alter these findings.

INTERPRETATION

In this prospective population-based cohort study, in a cohort largely on immunomodulatory therapy, higher 25-OH-D levels were associated with a reduced hazard of relapse. This occurred in a dose-dependent linear fashion, with each 10 nmol/l increase in 25-OH-D resulting in up to a 12% reduction in risk of relapse. Clinically, raising 25-OH-D levels by 50 nmol/l could halve the hazard of a relapse.

http://www.ncbi.nlm.nih.gov/pubmed/20695012

“In this prospective population-based cohort study, in a cohort largely on immunomodulatory therapy, higher 25-OH-D levels were associated with a reduced hazard of relapse.

This occurred in a dose-dependent linear fashion, with each 10 nmol/l increase in 25-OH-D resulting in up to a 12% reduction in risk of relapse.

Clinically, raising 25-OH-D levels by 50 nmol/l could halve the hazard of a relapse.”

“Half of the vegans were categorized as vitamin B12 deficient and would be expected to have a higher risk of developing clinical symptoms related to vitamin B12 deficiency.”

European Journal Of Clinical Nutrition • September 2010

Serum concentrations of vitamin B12 and folate in British male omnivores, vegetarians and vegans: results from a cross-sectional analysis of the EPIC-Oxford cohort study

Author information

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Abstract

BACKGROUND/OBJECTIVES

Vegans, and to a lesser extent vegetarians, have low average circulating concentrations of vitamin B12; however, the relation between factors such as age or time on these diets and vitamin B12 concentrations is not clear. The objectives of this study were to investigate differences in serum vitamin B12 and folate concentrations between omnivores, vegetarians and vegans and to ascertain whether vitamin B12 concentrations differed by age and time on the diet.

SUBJECTS/METHODS

A cross-sectional analysis involving 689 men (226 omnivores, 231 vegetarians and 232 vegans) from the European Prospective Investigation into Cancer and Nutrition Oxford cohort.

RESULTS

Mean serum vitamin B12 was highest among omnivores (281, 95% CI: 270-292 pmol/l), intermediate among vegetarians (182, 95% CI: 175-189 pmol/l) and lowest among vegans (122, 95% CI: 117-127 pmol/l). In all, 52% of vegans, 7% of vegetarians and one omnivore were classified as vitamin B12 deficient (defined as serum vitamin B12 <118 pmol/l). There was no significant association between age or duration of adherence to a vegetarian or a vegan diet and serum vitamin B12. In contrast, folate concentrations were highest among vegans, intermediate among vegetarians and lowest among omnivores, but only two men (both omnivores) were categorized as folate deficient (defined as serum folate <6.3 nmol/l).

CONCLUSION

Vegans have lower vitamin B12 concentrations, but higher folate concentrations, than vegetarians and omnivores. Half of the vegans were categorized as vitamin B12 deficient and would be expected to have a higher risk of developing clinical symptoms related to vitamin B12 deficiency.

Full text, graphs, charts and 48 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2933506/

Scandinavian Journal Of Primary Health Care • September 2010

Vitamin D status in patients with musculoskeletal pain, fatigue and headache: a cross-sectional descriptive study in a multi-ethnic general practice in Norway

Author information

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Abstract

OBJECTIVE
To investigate vitamin D levels in patients with non-specific musculoskeletal pain, headache, and fatigue.
DESIGN
A cross-sectional descriptive study.
SETTING
A health center in Oslo, Norway, with a multi-ethnic population.
SUBJECTS
A total of 572 patients referred by a general practitioner (GP) for an examination of hypovitaminosis D who reported musculoskeletal pain, headache, or fatigue. The patients' native countries were: Norway (n = 249), Europe, America, and South-East Asia (n = 83), and the Middle East, Africa, and South Asia (n = 240). Both genders and all ages were included.
MAIN OUTCOME MEASURES
Vitamin D levels (25-hydroxyvitamin D) in nmol/L.
RESULTS
Hypovitaminosis D (25-hydroxyvitamin D < 50 nmol/L) was found in 58% of patients. One-third of ethnic Norwegians had hypovitaminosis D, while 83% of patients from the Middle East, Africa, and South Asia had hypovitaminosis D with minimal seasonal variation of levels. One in two women from these countries had a vitamin D level below 25 nmol/L. Mean vitamin D level was lower in patients with headaches compared with patients with other symptoms. Some 15% of patients with low (< 50 nmol/L) vitamin D levels reported headaches, compared with 5% of those with normal vitamin D levels.
CONCLUSION
Our study shows a high prevalence of hypovitaminosis D in patients with non-specific musculoskeletal pain, headache, or fatigue for whom the GP had suspected a low vitamin D level. Hypovitaminosis D was not restricted to immigrant patients. These results indicate that GPs should maintain awareness of hypovitaminosis D and refer patients who report headaches, fatigue, and musculoskeletal pain with minimal sun exposure and a low dietary vitamin D intake for assessment.

http://www.ncbi.nlm.nih.gov/pubmed/20642395

"Our study shows a high prevalence of hypovitaminosis D in patients with non-specific musculoskeletal pain, headache, or fatigue for whom the General Practitioner had suspected a low vitamin D level.

Hypovitaminosis D was not restricted to immigrant patients. These results indicate that General Practitioners should maintain awareness of hypovitaminosis D and refer patients who report headaches, fatigue, and musculoskeletal pain with minimal sun exposure and a low dietary vitamin D intake for assessment."

“Serum methylmalonic acid and vitamin B(12) concentrations may be the more important risk factors for cognitive decline when compared to serum homocysteine concentrations, particularly in older populations exposed to food fortification and possible supplements containing folic acid.”

Neurology • January 2009

Biochemical indicators of vitamin B12 and folate insufficiency and cognitive decline

Tangney CC1, Tang Y, Evans DA, Morris MC.

Abstract

BACKGROUND

In some prospective studies, associations of serum vitamin B(12) and homocysteine concentrations with cognitive decline have been reported but few have examined the role of methylmalonic acid, a more specific marker of vitamin B(12) deficiency than homocysteine.

OBJECTIVE

The aim of the study was to determine whether serum concentrations of vitamin B(12) or selected metabolites are related to cognitive decline.

METHODS

A total of 516 subjects were selected in a stratified random sampling design from among Chicago Health and Aging Project participants for clinical evaluation. We used linear mixed models to examine the association of blood markers of vitamin B(12) status to change in cognitive scores over 6 years. Cognitive function was assessed every 3 years and measured as the sum of standardized scores on four tests.

RESULTS

Probable vitamin B(12) deficiency was observed in 14.2% of the sample. Elevated serum concentrations of homocysteine were present in 19.2% of subjects, and of methylmalonic acid, in 36.4%. Higher serum methylmalonic acid concentrations were predictive of faster rates of cognitive decline (beta = -0.00016, SE = 0.0001, p = 0.004) and higher serum vitamin B(12) concentrations were associated with slower rates of cognitive decline (beta = +0.00013, SE < 0.0001, p = 0.005) in multivariable adjusted mixed models. Serum concentrations of homocysteine had no relationship to cognitive decline.

CONCLUSIONS

Serum methylmalonic acid and vitamin B(12) concentrations may be the more important risk factors for cognitive decline when compared to serum homocysteine concentrations, particularly in older populations exposed to food fortification and possible supplements containing folic acid.

Full text, graphs, charts and 40 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2677500/

“A number of studies have reported inadequate intakes of n-3, folate, B vitamins, iron, and calcium in pregnant women. Depletion of nutrient reserves throughout pregnancy can increase a woman’s risk for maternal depression.”

Journal Of The American Dietetic Association • September 2009

Perinatal depression: prevalence, risks, and the nutrition link— a review of the literature

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Abstract

The purpose of this review is to examine the role of nutrition in perinatal depression. Perinatal (maternal) depression refers to major and minor episodes during pregnancy (termed antenatal) and/or within the first 12 months after delivery (termed postpartum or postnatal). Prevalence of antenatal depression can be as high as 20%, while approximately 12% to 16% of women experience postpartum depression. These are probably conservative estimates, as cases of maternal depression are underreported or underdiagnosed. Risk factors for depression include genetic predisposition and environmental factors, as well as a number of social, psychological, and biological factors. One biological factor given increasing consideration is inadequate nutrition. Credible links between nutrient deficiency and mood have been reported for folate, vitamin B-12, calcium, iron, selenium, zinc, and n-3 fatty acids. For maternal depression, the nutrient that has received the most attention from nutrition researchers has been the n-3 essential fatty acids. Numerous studies, such as randomized controlled trials, cohort studies, and ecological studies, have found a positive association between low n-3 levels and a higher incidence of maternal depression. In addition, nutrient inadequacies in pregnant women who consume a typical western diet might be much more common than researchers and clinicians realize. A number of studies have reported inadequate intakes of n-3, folate, B vitamins, iron, and calcium in pregnant women. Depletion of nutrient reserves throughout pregnancy can increase a woman’s risk for maternal depression.

http://www.ncbi.nlm.nih.gov/pubmed/19699836

“vitamin C and E prevents the smoke and X-ray-induced oxidative stress to strengthen antioxidant vitamin concentrations in the blood of the technicians.”

Cell Biochemistry And Function • October 2009

Vitamin C and E combination modulates oxidative stress induced by X-ray in blood of smoker and nonsmoker radiology technicians

Author information

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Abstract

X-ray radiation is detrimental to human cells and may lead to development of life-threatening diseases. Cigarette smoke contains about 500 chemicals that include organic and oxidant compounds whereas vitamin C and E (VCE) have scavenger effects on the compounds. We investigated effects of VCE administration on X-ray-induced oxidative toxicity in blood of smoker and nonsmoker X-ray technicians. Twenty technicians and 30 healthy age-matched subjects control were used in the study. Ten of the X-ray technicians and 15 of the control were smokers. Blood samples were taken from the control. Oral vitamin C (500 mg) and vitamin E (150 mg) were daily supplemented to the smoker and nonsmoker X-ray technicians for 5 weeks. Blood samples were taken from the X-ray technicians after and before 5 weeks. Plasma and erythrocytes lipid peroxidation (LP), reduced glutathione (GSH) levels, erythrocytes glutathione peroxidase (GSH-Px), and plasma antioxidant vitamin concentrations were investigated in control and X-ray technicians with smoker and nonsmoker. Plasma and erythrocytes LP levels were higher in the total X-ray group and smoker X-ray group than in control and nonsmoker X-ray group, respectively although the LP level was decreased by the VCE treatment. The plasma vitamin C, vitamin A, vitamin E, and beta-carotene concentrations were lower in the X-ray group than in control although their concentrations were increased by the treatment. The erythrocytes GSH level and GSH-Px activity were found to be higher in the treatment group than in the X-ray group. Plasma GSH level was not found to be different in all group. Reactive oxygen species may play role in the mechanism that has been proposed to explain the biological side effect of X-ray radiation and smoke. VCE prevents the smoke and X-ray-induced oxidative stress to strengthen antioxidant vitamin concentrations in the blood of the technicians.

http://www.ncbi.nlm.nih.gov/pubmed/19637207

“Vitamin D deficiency is associated with incident cardiovascular disease. Further clinical and experimental studies may be warranted to determine whether correction of vitamin D deficiency could contribute to the prevention of cardiovascular disease.”

Circulation • January 2008

Vitamin D deficiency and risk of cardiovascular disease

Author information

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Abstract

BACKGROUND

Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle, endothelium, and cardiomyocytes. A growing body of evidence suggests that vitamin D deficiency may adversely affect the cardiovascular system, but data from longitudinal studies are lacking.

METHODS AND RESULTS

We studied 1739 Framingham Offspring Study participants (mean age 59 years; 55% women; all white) without prior cardiovascular disease. Vitamin D status was assessed by measuring 25-dihydroxyvitamin D (25-OH D) levels. Prespecified thresholds were used to characterize varying degrees of 25-OH D deficiency (< 15 ng/mL, < 10 ng/mL). Multivariable Cox regression models were adjusted for conventional risk factors. Overall, 28% of individuals had levels < 15 ng/mL, and 9% had levels < 10 ng/mL. During a mean follow-up of 5.4 years, 120 individuals developed a first cardiovascular event. Individuals with 25-OH D < 15 ng/mL had a multivariable-adjusted hazard ratio of 1.62 (95% confidence interval 1.11 to 2.36, P=0.01) for incident cardiovascular events compared with those with 25-OH D > or = 15 ng/mL. This effect was evident in participants with hypertension (hazard ratio 2.13, 95% confidence interval 1.30 to 3.48) but not in those without hypertension (hazard ratio 1.04, 95% confidence interval 0.55 to 1.96). There was a graded increase in cardiovascular risk across categories of 25-OH D, with multivariable-adjusted hazard ratios of 1.53 (95% confidence interval 1.00 to 2.36) for levels 10 to < 15 ng/mL and 1.80 (95% confidence interval 1.05 to 3.08) for levels < 10 ng/mL (P for linear trend=0.01). Further adjustment for C-reactive protein, physical activity, or vitamin use did not affect the findings.

CONCLUSIONS

Vitamin D deficiency is associated with incident cardiovascular disease. Further clinical and experimental studies may be warranted to determine whether correction of vitamin D deficiency could contribute to the prevention of cardiovascular disease.

Full text with 58 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074622/

“Vitamin D insufficiency is common in patients with Type 2 diabetes during winter in Scotland. A single large dose of oral vitamin D2 improves endothelial function in patients with Type 2 diabetes and vitamin D insufficiency.”

Diabetic Medicine • March 2008

Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels

Author information

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Abstract

AIMS

To test whether a single large dose of vitamin D2 can improve endothelial function in patients with Type 2 diabetes mellitus and low serum 25-hydroxyvitamin D levels.

METHODS

Double-blind, parallel group, placebo-controlled randomized trial. A single dose of 100,000 IU vitamin D2 or placebo was administered to patients with Type 2 diabetes over the winter, when levels of circulating 25-hydroxyvitamin D were likely to be lowest. Patients were enrolled if their baseline 25-hydroxyvitamin D level was < 50 nmol/l. Endothelial function and blood pressure were measured and fasting blood samples were taken at baseline and 8 weeks after administration of vitamin D.

RESULTS

Forty-nine per cent of subjects screened had 25-hydroxyvitamin D levels < 50 nmol/l. Thirty-four subjects completed the study, with a mean age of 64 years and a baseline 25-hydroxyvitamin D level of 38.3 nmol/l. Vitamin D supplementation increased 25-hydroxyvitamin D levels by 15.3 nmol/l relative to placebo and significantly improved flow mediated vasodilatation (FMD) of the brachial artery by 2.3%. The improvement in FMD remained significant after adjusting for changes in blood pressure. Vitamin D supplementation significantly decreased systolic blood pressure by 14 mmHg compared with placebo; this did not correlate with change in FMD.

CONCLUSIONS

Vitamin D insufficiency is common in patients with Type 2 diabetes during winter in Scotland. A single large dose of oral vitamin D2 improves endothelial function in patients with Type 2 diabetes and vitamin D insufficiency.

http://www.ncbi.nlm.nih.gov/pubmed/18279409

Journal Of The American Medical Directors Association • March 2008

Do acid-lowering agents affect vitamin B12 status in older adults?

Author information
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Abstract

OBJECTIVE

To examine the relationship between serum vitamin B12 levels in older adults on histamine(2) receptor antagonists (H2 blockers) or proton-pump inhibitors (PPI) over 6 years.

PARTICIPANTS

A cross-sectional sample of 659 adults, 60 to 102 years, from long-term care facilities and community ambulatory care (C) in the Bronx.

MEASUREMENTS

Patient demographics, serum B12 levels, use and duration of use of H2 blockers, PPIs, antacids, multivitamin/minerals, liquid dietary supplements, oral vitamin B12 supplementation, oral or intramuscular B12 therapy, and recent lab chemistries.

RESULTS

Acid-lowering agents (ALA) were used by 54% (PPIs by 26% and H2 blockers by 28%), duration averaged 18.2 +/- 16.0 (SD) months. NH and C subjects had similar ages ($P = .9971$), gender distributions ($P = .625$), durations of ALA use ($P = .1227$), and rates of PPI use ($P = .130$); NH subjects used more H2 blockers ($P < .0005$) and had less low B12 status ($P = .037$). H2 blocker use did not influence serum B12 status ($P = .1036$) while PPI use was associated with diminished serum B12 levels ($P < .00005$). Concomitant oral B12 supplementation slowed but did not prevent the decline in B12 status during prolonged PPI use ($P = .0125$).

CONCLUSIONS

B12 status declines during prolonged PPI use in older adults, but not with prolonged H2 blocker use; supplementation with RDA amounts of B12 do not prevent this decline. This report reinforces that B12 deficiency is common in the elderly and suggests that it appears prudent to monitor periodically B12 status while on prolonged PPI use, to enable correction before complications ensue.

http://www.ncbi.nlm.nih.gov/pubmed/18294598

“Vitamin D deficiency is now recognized as a pandemic.
The major cause of vitamin D deficiency is the lack of appreciation that sun exposure in moderation is the major source of vitamin D for most humans. Very few foods naturally contain vitamin D, and foods that are fortified with vitamin D are often inadequate to satisfy either a child’s or an adult’s vitamin D requirement.”

American Journal Of Clinical Nutrition • April 2008

Vitamin D deficiency: a worldwide problem with health consequences

Author information

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Abstract

Vitamin D deficiency is now recognized as a pandemic. The major cause of vitamin D deficiency is the lack of appreciation that sun exposure in moderation is the major source of vitamin D for most humans. Very few foods naturally contain vitamin D, and foods that are fortified with vitamin D are often inadequate to satisfy either a child’s or an adult’s vitamin D requirement. Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults. Vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension, and infectious diseases. A circulating level of 25-hydroxyvitamin D of >75 nmol/L, or 30 ng/mL, is required to maximize vitamin D’s beneficial effects for health. In the absence of adequate sun exposure, at least 800-1000 IU vitamin D3/d may be needed to achieve this in children and adults. Vitamin D2 may be equally effective for maintaining circulating concentrations of 25-hydroxyvitamin D when given in physiologic concentrations.

http://www.ncbi.nlm.nih.gov/pubmed/18400738

“Throughout the life cycle the skeleton requires optimum development and maintenance of its integrity to prevent fracture. Bones break because the loads placed on them exceed the ability of the bone to absorb the energy involved. It is now estimated that one in three women and one in twelve men aged >55 years will suffer from osteoporosis in their lifetime ...”

Proceedings Of The Nutritional Society • May 2008

Importance of calcium, vitamin D and vitamin K for osteoporosis prevention and treatment

Author information

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Abstract

Throughout the life cycle the skeleton requires optimum development and maintenance of its integrity to prevent fracture. Bones break because the loads placed on them exceed the ability of the bone to absorb the energy involved. It is now estimated that one in three women and one in twelve men aged >55 years will suffer from osteoporosis in their lifetime and at a cost in the UK of > 1.7 pounds x 10(9) per year. The pathogenesis of osteoporosis is multifactorial. Both the development of peak bone mass and the rate of bone loss are determined by key endogenous and exogenous factors. Ca supplements appear to be effective in reducing bone loss in women late post menopause (>5 years post menopause), particularly in those with low habitual Ca intake (<400 mg/d). In women early post menopause (<5 years post menopause) who are not vitamin D deficient, Ca supplementation has little effect on bone mineral density. However, supplementation with vitamin D and Ca has been shown to reduce fracture rates in the institutionalised elderly, but there remains controversy as to whether supplementation is effective in reducing fracture in free-living populations. Re-defining vitamin D requirements in the UK is needed since there is evidence of extensive hypovitaminosis D in the UK. Low vitamin D status is associated with an increased risk of falling and a variety of other health outcomes and is an area that requires urgent attention. The role of other micronutrients on bone remains to be fully defined, although there are promising data in the literature for a clear link between vitamin K nutrition and skeletal integrity, including fracture reduction.

http://www.ncbi.nlm.nih.gov/pubmed/18412990

“Deficiencies of folate or of vitamin B12 are widespread and constitute a major global burden of morbidity affecting all age groups. Detecting or confirming the presence of folate or vitamin B12 deficiency and distinguishing one from the other depends, ultimately, on laboratory testing.”

Food Nutrition Bulletin • June 2008

Indicators for assessing folate and vitamin B12 status and for monitoring the efficacy of intervention strategies

Author information

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Abstract

Deficiencies of folate or of vitamin B12 are widespread and constitute a major global burden of morbidity affecting all age groups. Detecting or confirming the presence of folate or vitamin B12 deficiency and distinguishing one from the other depends, ultimately, on laboratory testing. Tests to determine the presence of folate or vitamin B12 deficiency are used singly or in combination to establish the nutritional status and prevalence of deficiencies of the vitamins in various populations. The efficacy of interventions through the use of fortification or supplements is monitored using the same laboratory tests. Tests currently in use have limitations that can be either technical or have a biological basis. Consequently, each single test cannot attain perfect sensitivity, specificity, or predictive value. Laboratory indicators of vitamin B12 or folate status involve measurement of either the total or a physiologically relevant fraction of the vitamin in a compartment such as the blood. Thus, assays to measure vitamin B12 or folate in plasma or serum as well as folate in red blood cells are in widespread use, and more recently, methods to measure vitamin B12 associated with the plasma binding protein transcobalamin (holotranscobalamin) have been developed. Alternatively, levels of surrogate biochemical markers that reflect the metabolic function of the vitamin can be used. Surrogates most commonly used are plasma homocysteine, for detection of either vitamin B12 or folate deficiency and methylmalonic acid for detection of vitamin B12 deficiency. The general methods as well as their uses, indications, and limitations are presented.

http://www.ncbi.nlm.nih.gov/pubmed/18709881

Food Nutrition Bulletin • June 2008

Causes of vitamin B12 and folate deficiency

Author information

By L.H. Allen

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Abstract

"This review describes current knowledge of the main causes of vitamin B12 and folate deficiency. The most common explanations for poor vitamin B12 status are a low dietary intake of the vitamin (i.e., a low intake of animal-source foods) and malabsorption. Although it has long been known that strict vegetarians (vegans) are at risk for vitamin B12 deficiency, evidence now indicates that low intakes of animal-source foods, such as occur in some lacto-ovo vegetarians and many less-industrialized countries, cause vitamin B12 depletion. Malabsorption of the vitamin is most commonly observed as food-bound cobalamin malabsorption due to gastric atrophy in the elderly, and probably as a result of Helicobacter pylori infection. There is growing evidence that gene polymorphisms in transcobalamins affect plasma vitamin B12 concentrations. The primary cause of folate deficiency is low intake of sources rich in the vitamin, such as legumes and green leafy vegetables, and the consumption of these foods may explain why folate status can be adequate in relatively poor populations. Other situations in which the risk of folate deficiency increases include lactation and alcoholism."

http://www.ncbi.nlm.nih.gov/pubmed/18709879

Current Rheumatology Reports • August 2008

The link between vitamin D deficiency and systemic lupus erythematosus

Author information

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Abstract

“Vitamin D deficiency is highly prevalent and is increasingly thought to be an important risk factor in many diseases that have high morbidity and mortality, including lupus. Vitamin D is an immunomodulatory hormone with effects on T cells, B cells, and dendritic cells. Animal models of autoimmune disease and epidemiologic studies suggest a role for vitamin D as a modifiable environmental factor in autoimmune disease. Recommendations are available regarding screening for and repletion of vitamin D deficiency. More research is needed to understand the role of vitamin D as an immunomodulator and to determine the optimal range of serum 25-hydroxyvitamin D for musculoskeletal, cardiovascular, and immune health.”

http://www.ncbi.nlm.nih.gov/pubmed/18662506

Current Opinions In Rheumatology • September 2008

Vitamin D in systemic lupus erythematosus

Author information

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Abstract

PURPOSE OF REVIEW

There is growing interest in the contribution of vitamin D deficiency to autoimmunity. It is therefore timely to review the immunologic actions of vitamin D and the evidence linking vitamin D deficiency to autoimmune disease in animal models and to systemic lupus erythematosus in epidemiologic studies.

RECENT FINDINGS

A number of recent studies have highlighted the association between systemic lupus erythematosus and vitamin D deficiency. Vitamin D deficiency skews the immunologic response towards loss of tolerance. Adding vitamin D in vitro reverses immunologic abnormalities characteristic of systemic lupus erythematosus.

SUMMARY

Multiple systemic lupus erythematosus cohorts have low vitamin D levels. The physiologic and clinical consequences of vitamin D deficiency in systemic lupus erythematosus are not entirely known. Prospective studies of vitamin D in systemic lupus erythematosus are limited, but most cross-sectional studies show an inverse relationship between levels of vitamin D and disease activity. This suggests that repletion of vitamin D may have benefits beyond bone health for patients with systemic lupus erythematosus.

http://www.ncbi.nlm.nih.gov/pubmed/18698173

Nutrition Review • October 2008

Vitamin D: a D-Lightful health perspective

By M.F. Holick

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Abstract

"Sunlight provides most humans with their vitamin D requirement. Adequate vitamin D(3) by synthesis in the skin or from dietary and supplemental sources is essential for bone health throughout life. Vitamin D deficiency is defined as a 25(OH)D concentration <20 ng/mL (50 nmol/L); vitamin D sufficiency as a 25(OH)D >30 ng/mL (75 nmol/L), and insufficiency as 21-29 ng/mL. Vitamin D deficiency and insufficiency has been linked to a wide variety of chronic diseases including common cancers, autoimmune, cardiovascular, and infectious diseases. **Healthcare professionals need to be aware of the vitamin D deficiency pandemic**. Guidelines for sensible sun exposure and supplemental vitamin D of 800-1000 IU/day are needed."

http://www.ncbi.nlm.nih.gov/pubmed/18844847

“These revised guidelines for vitamin D intake for healthy infants, children, and adolescents are based on evidence from new clinical trials and the historical precedence of safely giving 400 IU of vitamin D per day in the pediatric and adolescent population. New evidence supports a potential role for vitamin D in maintaining innate immunity and preventing diseases such as diabetes and cancer. The new data may eventually refine what constitutes vitamin D sufficiency or deficiency.”

Pediatrics • November 2008

Prevention of rickets and vitamin D deficiency in infants, children, and adolescents

Author information

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Collaborators (25)

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Abstract

Rickets in infants attributable to inadequate vitamin D intake and decreased exposure to sunlight continues to be reported in the United States. There are also concerns for vitamin D deficiency in older children and adolescents. Because there are limited natural dietary sources of vitamin D and adequate sunshine exposure for the cutaneous synthesis of vitamin D is not easily determined for a given individual and may increase the risk of skin cancer, the recommendations to ensure adequate vitamin D status have been revised to include all infants, including those who are exclusively breastfed and older children and adolescents. It is now recommended that all infants and children, including adolescents, have a minimum daily intake of 400 IU of vitamin D beginning soon after birth. The current recommendation replaces the previous recommendation of a minimum daily intake of 200 IU/day of vitamin D supplementation beginning in the first 2 months after birth and continuing through adolescence. These revised guidelines for vitamin D intake for healthy infants, children, and adolescents are based on evidence from new clinical trials and the historical precedence of safely giving 400 IU of vitamin D per day in the pediatric and adolescent population. New evidence supports a potential role for vitamin D in maintaining innate immunity and preventing diseases such as diabetes and cancer. The new data may eventually refine what constitutes vitamin D sufficiency or deficiency.

http://www.ncbi.nlm.nih.gov/pubmed/18977996

“Vitamin D insufficiency is prevalent in ambulatory, and especially obese, elderly living in Denver, Colorado, despite vitamin D intake consistent with national recommendations. Dietary intake of vitamin D appeared to be unreliable to prevent insufficiency. Based on our results, along with other published data, we feel that national recommendations for vitamin D intake in the elderly should be increased to at least 800 to 1000 IU/d of over-the-counter supplemental cholecalciferol.”

American Journal Of Geriatric Pharmacotherapy • March 2007

Prevalence of vitamin D insufficiency in elderly ambulatory outpatients in Denver, Colorado

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Abstract

BACKGROUND

Vitamin D insufficiency is common in the elderly. However, previous studies have utilized 25-hydroxvvitamin D (25[OH]D) concentrations as low as <16 ng/mL for defining vitamin D insufficiency. Moreover, most of the studies have been conducted in European patients, in certain geographic areas of the United States, or in institutionalized elderly.

OBJECTIVE

The goal of this study was to characterize vitamin D concentrations in ambulatory elderly living in metropolitan Denver, Colorado, utilizing 25(OH)D concentrations <32 ng/mL as the definition for vitamin D insufficiency.

METHODS

Ambulatory older adults (aged 65-89 years) with clinic visits during December 2005 and January 2006 were enrolled. Serum concentrations of 25(OH)D, parathyroid hormone (PTH), calcium, phosphorus, creatinine, and albumin were measured; height and weight were also measured. Data regarding dietary and over-the-counter vitamin D intake were collected, as well as information on body mass index, history of osteoporosis, osteoporosis treatment, and history of falls and fractures.

RESULTS

Eighty patients (mean [SD] age, 77.8 [5.3] years; age range, 66-89 years) completed the study; there were no dropouts. The majority of patients were white (88%) and female (68%). Fifty-nine (74%) were found to have vitamin D insufficiency. Mean total and over-the-counter vitamin D intake was significantly higher in sufficient ($P < 0.01$) and insufficient ($P < 0.05$) patients compared with deficient patients, but dietary intake did not differ significantly between groups. The majority of patients who were vitamin D insufficient consumed more than the recommended 400 to 600 IU/d of vitamin D. Obese patients were found to have significantly lower 25(OH)D concentrations ($P < 0.001$) and higher PTH concentrations ($P = 0.04$) than nonobese patients.

CONCLUSIONS

Vitamin D insufficiency is prevalent in ambulatory, and especially obese, elderly living in Denver, Colorado, despite vitamin D intake consistent with national recommendations. Dietary intake of vitamin D appeared to be unreliable to prevent insufficiency. Based on our results, along with other published data, we feel that national recommendations for vitamin D intake in the elderly should be increased to at least 800 to 1000 IU/d of over-the-counter supplemental cholecalciferol.

http://www.ncbi.nlm.nih.gov/pubmed/17608242

Progress In Biophysics And Molecular Biology • September 2006

Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease

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Abstract

"Autoimmune diseases like multiple sclerosis (MS) and inflammatory bowel disease (IBD) occur because of an inappropriate immune-mediated attack against self-tissue. Analyses of genetically identical twins shows that besides genetics there are important environmental factors that contribute to MS and IBD development. Vitamin D availability due to sunshine exposure or diet may play a role in the development of MS and IBD. Compelling data in mice show that vitamin D and signaling through the vitamin D receptor dictate the outcome of experimental MS and IBD. Furthermore, the evidence points to the direct and indirect regulation of T cell development and function by vitamin D. In the absence of vitamin D and signals delivered through the vitamin D receptor, auto reactive T cells develop and in the presence of active vitamin D (1,25(OH)(2)D(3)) and a functional vitamin D receptor the balance in the T cell response is restored and autoimmunity avoided."

http://www.ncbi.nlm.nih.gov/pubmed/16563470

“As a consequence, legislation has to be changed to allow higher amounts of vitamin D in fortified foods and supplements.”

Progress In Biophysics And Molecular Biology • September 2006

Vitamin D and disease prevention with special reference to cardiovascular disease

Author information

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Abstract

Circulating 25-hydroxyvitamin D [25(OH)D] is the hallmark for determining vitamin D status. Serum parathyroid hormone [PTH] increases progressively when 25(OH)D falls below 75 nmol/l. Concentrations of 25(OH)D below 50 nmol/l or even below 25 nmol/l are frequently observed in various population groups throughout the world. This paper highlights the relationship of vitamin D insufficiency with cardiovascular disease and non-insulin dependent diabetes mellitus, two diseases that account for up to 50% of all deaths in western countries. There is evidence from patients with end-stage renal disease that high PTH concentrations are causally related to cardiovascular morbidity and mortality. Activated vitamin D is able to increase survival in this patient group significantly. Moreover, already slightly enhanced PTH concentrations are associated with ventricular hypertrophy and coronary heart disease in the general population. Experimental studies have demonstrated that a lack of vitamin D action leads to hypertension in mice. Some intervention trials have also shown that vitamin D can reduce blood pressure in hypertensive patients. In young and elderly adults, serum 25(OH)D is inversely correlated with blood glucose concentrations and insulin resistance. Sun-deprived lifestyle, resulting in low cutaneous vitamin D synthesis, is the major factor for an insufficient vitamin D status. Unfortunately, vitamin D content of most foods is negligible. Moreover, fortified foods and over-the-counter supplements usually contain inadequate amounts of vitamin D to increase serum 25(OH)D to 75 nmol/l. As a consequence, legislation has to be changed to allow higher amounts of vitamin D in fortified foods and supplements.

http://www.ncbi.nlm.nih.gov/pubmed/16600341

“On the basis of current data, we suggest that oral doses of both folic acid (800 microg daily) and vitamin B12 (1 mg daily) should be tried to improve treatment outcome in depression.”

Journal Of Psychopharmacology • January 2005

Treatment of depression: time to consider folic acid and vitamin B12

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Abstract

We review the findings in major depression of a low plasma and particularly red cell folate, but also of low vitamin B12 status. Both low folate and low vitamin B12 status have been found in studies of depressive patients, and an association between depression and low levels of the two vitamins is found in studies of the general population. Low plasma or serum folate has also been found in patients with recurrent mood disorders treated by lithium. A link between depression and low folate has similarly been found in patients with alcoholism. It is interesting to note that Hong Kong and Taiwan populations with traditional Chinese diets (rich in folate), including patients with major depression, have high serum folate concentrations. However, these countries have very low life time rates of major depression. Low folate levels are furthermore linked to a poor response to antidepressants, and treatment with folic acid is shown to improve response to antidepressants. A recent study also suggests that high vitamin B12 status may be associated with better treatment outcome. Folate and vitamin B12 are major determinants of one-carbon metabolism, in which S-adenosylmethionine (SAM) is formed. SAM donates methyl groups that are crucial for neurological function. Increased plasma homocysteine is a functional marker of both folate and vitamin B12 deficiency. Increased homocysteine levels are found in depressive patients. In a large population study from Norway increased plasma homocysteine was associated with increased risk of depression but not anxiety. There is now substantial evidence of a common decrease in serum/red blood cell folate, serum vitamin B12 and an increase in plasma homocysteine in depression. Furthermore, the MTHFR C677T polymorphism that impairs the homocysteine metabolism is shown to be overrepresented among depressive patients, which strengthens the association. On the basis of current data, we suggest that oral doses of both folic acid (800 microg daily) and vitamin B12 (1 mg daily) should be tried to improve treatment outcome in depression.

http://www.ncbi.nlm.nih.gov/pubmed/15671130

“Cobalamin [B12] deficiency is a common finding.
In the elderly the prevalence is 10-20%, but only 5-10% of these are clinically symptomatic.
Typical clinical symptoms include macrocytic anemia, neuropsychiatric symptoms and glossitis.
In many cases this triad is lacking, however. The serum cobalamin assay is the best first line test,
but the results must be carefully interpreted, since a normal level does not exclude deficiency.”

Wiener Klinische Wochenschrift • September 2005

Vitamin B12 deficiency. New data on an old theme

Author information

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Abstract

Cobalamin deficiency is a common finding. In the elderly the prevalence is 10-20%, but only 5-10% of these are clinically symptomatic. Typical clinical symptoms include macrocytic anemia, neuropsychiatric symptoms and glossitis. In many cases this triad is lacking, however. The serum cobalamin assay is the best first line test, but the results must be carefully interpreted, since a normal level does not exclude deficiency. Markers of cobalamin activity, such as serum homocysteine or methylmalonic acid may be helpful in this situation. The main cause of cobalamin deficiency is atrophic gastritis. It is either caused by an autoimmune process which leads to achlorhydria and severe intrinsic factor deficiency (“classical pernicious anemia”) or by atrophic gastritis from other causes, in particular helicobacter pylori infection. In the latter cases the lack of gastric acid does not allow separation of cobalamin from proteins, but intrinsic factor, although low, is sufficient for cobalamin protection (food cobalamin malabsorption). Helicobacter pylori eradication may cure some of these patients. While in food cobalamin malabsorption syndrome small doses of oral cobalamin are effective, parenteral therapy or high oral doses are required for treatment of pernicious anemia. While almost all patients respond hematologically, only half of the patients with neurological signs, and a small minority of psychiatric patients respond to treatment. Patients with pernicious anemia and atrophic gastritis have a greatly increased long-term risk for gastric carcinoids.

http://www.ncbi.nlm.nih.gov/pubmed/16395986

“These results show that greater calcium consumption and a Calcium/Potassium ratio of >0.74 are associated with better bone mineral density values in young women, and that milk is the lactic product best associated with good bone health.”

Archivos Latinoamericanos de Nutricion • June 2004

The influence of calcium and phosphorus intake on bone mineral density in young women

Author information

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Abstract

The threat of osteoporosis in later life means that the bone mass women achieve during their youth is important. Eighty seven women aged 18-35 y from the Madrid region were studied to determine the relationship between their calcium, phosphorus and milk product intakes and bone mineral density (BMD). Intakes of these items were moniroed using a three day food intake record. BMD was measured by double photonic densitometry of the lumbar region, hip and right forearm. Mean calcium intake (802.1+/-258.7 mg/day) was less than that recommended for 45% of women. A linear, positive correlation was seen between calcium intake and BMD at the hip (r=0.23) and greater trochanter (r=0.24) (p<0.05). Women whose calcium intake was >1000 mg/day had greater hip BMDs than those whose intake was below this level (0.97+/-0.11 g/cm2 compared to 0.90+/-0.10 g/cm2). Similar results were seen for the femur head and greater trochanter in subjects whose Ca/P ratio was >0.74 (50th percentile). In addition, an intake of more than two rations of milk per day was optimum for achieving adequate bone mass in different areas of the hip. These results show that greater calcium consumption and a Ca/P ratio of >0.74 are associated with better BMD values in young women, and that milk is the lactic product best associated with good bone health.

http://www.ncbi.nlm.nih.gov/pubmed/15586689

American Journal Of Clinical Nutrition • October 2004

Dairy intakes affect bone density in the elderly

Author information

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Abstract

BACKGROUND

Race and sex differences in the effect of diet on bone mineral density (BMD) at the hip in the elderly are unknown.

OBJECTIVES

This study related cross-sectional nutrient and dairy product consumption to hip BMD in white and black men and women aged >60 y and evaluated the influence of nutrient and dairy product consumption on changes in BMD in a white cohort participating in a calcium, vitamin D, or placebo trial.

DESIGN

The Health Habits and History Questionnaire was used in 289 white women and 116 white men who participated in the trial and in 265 black women and 75 black men to predict total hip and femoral neck BMD or changes in BMD.

RESULTS

Blacks had higher calcium intakes than did whites (700 and 654 mg/d, respectively; P = 0.0094), and men had higher calcium intakes than did women (735 and 655 mg/d, respectively; P = 0.0007). For men, the correlation between total hip BMD and dairy calcium intake after adjustment for age, race, and weight was 0.23 (P < 0.005); this relation was not significant in women (r = 0.02, P = 0.12). Similar results were found for femoral neck BMD. In the longitudinal study, calcium supplementation reduced bone loss from the total hip and femoral neck in those who consumed <1.5 servings of dairy products/d and were <72 y old.

CONCLUSIONS

Cross-sectional results indicated that higher dairy product consumption is associated with greater hip BMD in men, but not in women. Calcium supplementation protected both men and women from bone loss in the longitudinal study of whites.

Full text, graphs, charts and 17 references

http://ajcn.nutrition.org/content/80/4/1066.long

“Cross-sectional results indicated that higher dairy product consumption is associated with greater hip bone mineral density in men, but not in women.

Calcium supplementation protected both men and women from bone loss in the longitudinal study of whites.”

Experimental Biology And Medicine • December 2004

Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence

Author information

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Abstract

"Low vitamin D status has been implicated in the etiology of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, and inflammatory bowel disease. The optimal level of vitamin D intake required to support optimal immune function is not known but is likely to be at least that required for healthy bones. Experimentally, vitamin D deficiency results in the increased incidence of autoimmune disease. Mechanistically, the data point to a role for vitamin D in the development of self-tolerance. The vitamin D hormone (1,25-dihydroxy vitamin D(3)) regulates T helper cell (Th1) and dendritic cell function while inducing regulatory T-cell function. The net result is a decrease in the Th1-driven autoimmune response and decreased severity of symptoms. This review discusses the accumulating evidence pointing to a link between vitamin D and autoimmunity. Increased vitamin D intakes might decrease the incidence and severity of autoimmune diseases and the rate of bone fracture."

http://www.ncbi.nlm.nih.gov/pubmed/15564440

American Journal Of Clinical Nutrition • December 2004

Vitamin D status, 1,25-dihydr0oxyvitamin D3, and the immune system

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Abstract

“Vitamin D is an important immune system regulator. The active form of vitamin D, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], has been shown to inhibit the development of autoimmune diseases, including inflammatory bowel disease (IBD). Paradoxically, other immune system-mediated diseases (experimental asthma) and immunity to infectious organisms were unaffected by 1,25(OH)2D3 treatment. There are similar paradoxical effects of vitamin D deficiency on various immune system functions. Vitamin D and vitamin D receptor (VDR) deficiency resulted in accelerated IBD. Experimental asthma was unaffected by 1,25(OH)2D3 treatment and was less severe among VDR-deficient mice. Vitamin D is a selective regulator of the immune system, and the outcome of 1,25(OH)2D3 treatment, vitamin D deficiency, or VDR deficiency depends on the nature of the immune response (eg, infectious disease, asthma, or autoimmune disease). An additional factor that determines the effect of vitamin D status on immune function is dietary calcium. Dietary calcium has independent effects on IBD severity. Vitamin D-deficient mice on low-calcium diets developed the most severe IBD, and 1,25(OH)2D3 treatment of mice on low-calcium diets improved IBD symptoms. However, the best results for IBD were observed when the calcium concentration was high and 1,25(OH)2D3 was administered. Both the type of immune response and the calcium status of the host determine the effects of vitamin D status and 1,25(OH)2D3 on immunity.”

Full text with 34 references

http://ajcn.nutrition.org/content/80/6/1717S.full.pdf

“In individuals 9 yrs and older, 3-4 servings of dairy products are needed to meet or exceed the Calcium Adequate Intake and to ensure a low prevalence of inadequate Calcium intake.”

Journal Of The American College Of Nutrition • December 2004

Determination of the optimal number of dairy servings to ensure a low prevalence of inadequate calcium intake in Americans

Author information

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Abstract

BACKGROUND

Many Americans are not getting the recommended amounts of calcium in their diet. Since dairy foods provide most of the calcium in the diet, the number of recommended servings of dairy products may need to be revised.

OBJECTIVE

1. To determine the calcium intake of various age groups that met or exceeded the intake of dairy products recommended by the Food Guide Pyramid (FGP). 2. To determine the optimal level of dairy consumption that ensures a low prevalence of inadequate calcium (Ca) intake by Americans.

METHODS

Using data from the Continuing Survey of Food Intake by Individuals, 1994-96, 1998, (CSFII) and the National Health and Nutrition Examination Survey, 1999-2000 (NHANES) we determined the calcium intake in individuals who met the recommended daily dairy servings as well as the minimum number of dairy servings required for the mean Ca intake of various age groups to exceed their respective Adequate Intakes (AI).

RESULTS

Objective 1: Meeting or exceeding the FGP dairy recommendation led to calcium intakes that met recommended levels. However, very few individuals in all age groups met or exceeded the number of dairy servings recommended by FGP. Objective 2: Results indicated that in children 2-8 yrs, 2 dairy servings/d were required for the mean Ca intake (835 +/- 72 and 822 +/- 68 mg/d, in CSFII and NHANES IV, respectively) to exceed the AI. In children 9-18 yrs, 4 dairy servings/d) were required for the mean Ca intake of the group (1540 +/- 93 and 1518 +/- 86 mg/d) to exceed the AI. Similar data were observed in adults 19+ yrs, e.g., in adults 51+ yrs, 3 dairy servings/d were required for the mean Ca intake of the group (1241 +/- 53 and 1217 +/- 53 mg/d) to exceed the AI.

CONCLUSION

Groups that met or exceeded the FGP dairy recommendations were more likely to have a mean calcium intake above the AI but had an average intake of about one serving higher than current recommendations. In individuals 9 yrs and older, 3-4 servings of dairy products are needed to meet or exceed the Ca AI and to ensure a low prevalence of inadequate Ca intake.

http://www.ncbi.nlm.nih.gov/pubmed/15637213

“Various studies have documented that both DHA and vitamin A are vital for optimal visual and neural development and function. There is a need for further investigations to elucidate how vitamin A deficiency reduces membrane DHA level, and to delineate the **synergistic** effect of the two nutrients on vision, learning and memory.”

Prostaglandins, Leukotrienes And Essential Fatty Acids • December 2004

Vitamin A deficiency reduces liver and colon docosahexaenoic acid levels in rats fed high linoleic and low alpha-linolenic acid diet

Author information

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Abstract

Studies indicate that the transcription factor peroxisome proliferator-activated receptors (PPARs) regulate the activity of delta-6 and -5 desaturases and several key enzymes of peroxisomal beta-oxidation, including acyl-CoA oxidase. These enzymes are vital for the synthesis of docosahexaenoic (22:6 omega 3; DHA) and osbond (22:5 omega 6, OA) acids. An activated PPAR must form a hetrodimer with the obligate cofactor retinoid X receptor (RXR) to interact with a peroxisome proliferator responsive element (PPRE) of a target gene and to regulate transcriptional expression. The vitamin A metabolite, 9-cis retinoic acid, is the most potent ligand of RXR. We have tested the possibility that deficiency of vitamin A would compromise tissue levels of both DHA and OA in rats. Two groups of male Wistar rats were randomly distributed to receive vitamin A deficient (VAD) or sufficient (VAS) diet. After seven weeks of feeding, the rats were killed and colon and liver tissues removed for the analysis of fatty acids and antioxidant status. The VAD compared to the VAS rats had elevated levels of arachidonic (AA, $P<0.001$), adrenic acid (22:4 omega 6, $P<0.005$) and OA ($P<0.0001$) and reduced proportions of eicosapentaenoic (EPA, docosapentaenoic (DPA), DHA and total omega 3 fatty ($P<0.0001$) in colon choline phosphoglycerides (CPG). Similarly, liver CPG of the VAD rats had higher AA and adrenic acid and OA ($P<0.0001$), and lower EPA, DPA and DHA ($P<0.0001$) than the VAS rats. There was a similar fatty acid pattern in ethanolamine phosphoglycerides of the colon and liver tissues. These differences could not be explained by the conventional microsomal-peroxisomal pathway of the synthesis of the long-chain omega 6 and omega 3 polyunsaturated fatty acids. We postulate that deficiency of dietary vitamin A and the consequential depletion of retinoids inhibits DHA, and enhances OA, synthesis by differential effects on the independent synthetic pathways of the two fatty acids in the mitochondria. Various studies have documented that both DHA and vitamin A are vital for optimal visual and neural development and function. There is a need for further investigations to elucidate how vitamin A deficiency reduces membrane DHA level, and to delineate the synergistic effect of the two nutrients on vision, learning and memory.

http://www.ncbi.nlm.nih.gov/pubmed/15519497

Journal Of The American College Of Cardiology • January 2003

Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure?

Author information

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Abstract

OBJECTIVES

This study was designed to evaluate the association between vitamin D status and congestive heart failure (CHF).

BACKGROUND

Impaired intracellular calcium metabolism is an important factor in the pathogenesis of CHF. The etiology of CHF, however, is not well understood.

METHODS

Twenty patients age <50 years and 34 patients age >/=50 years with New York Heart Association classes >/=2 and 34 control subjects age >/=50 years were recruited. N-terminal pro-atrial natriuretic peptide (NT-proANP), a predictor of CHF severity; vitamin D metabolites; and parameters of calcium metabolism were measured in fasting blood samples collected between November 2000 and March 2001.

RESULTS

Both groups of CHF patients had markedly increased serum levels of NT-proANP ($p < 0.001$), increased serum phosphorus levels ($p < 0.001$), and reduced circulating levels of both 25-hydroxyvitamin D ($p < 0.001$) and calcitriol ($p < 0.001$). Albumin-corrected calcium levels were reduced and parathyroid hormone levels were increased in the younger CHF patients compared with the controls (both p values <0.001). Moreover, parathyroid hormone levels tended to be higher in the elderly CHF patients than in the controls ($p = 0.074$). In a nonlinear regression analysis 25-hydroxyvitamin D and calcitriol were inversely correlated with NT-proANP ($r(2) = 0.16$; $p < 0.001$ and $r(2) = 0.12$; $p < 0.01$, respectively). The vitamin D genotype at the BmsI restriction site did not differ between the study groups.

CONCLUSIONS

The low vitamin D status can explain alterations in mineral metabolism as well as myocardial dysfunction in the CHF patients, and it may therefore be a contributing factor in the pathogenesis of CHF.

Full text, graphs, charts and 45 references

http://www.sciencedirect.com/science/article/pii/S0735109702026244

“The low vitamin D status can explain alterations in mineral metabolism as well as myocardial dysfunction in the congestive heart failure patients, and it may therefore be a contributing factor in the pathogenesis of congestive heart failure.”

American Family Physicians • March 2003

Vitamin B12 deficiency

Author information

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Abstract

“Vitamin B12 (cobalamin) deficiency is a common cause of macrocytic anemia and has been implicated in a spectrum of neuropsychiatric disorders. The role of B12 deficiency in hyperhomocysteinemia and the promotion of atherosclerosis is only now being explored. Diagnosis of vitamin B12 deficiency is typically based on measurement of serum vitamin B12 levels; however, about 50 percent of patients with subclinical disease have normal B12 levels. A more sensitive method of screening for vitamin B12 deficiency is measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B12 deficiency. Use of the Schilling test for detection of pernicious anemia has been supplanted for the most part by serologic testing for parietal cell and intrinsic factor antibodies. Contrary to prevailing medical practice, studies show that supplementation with oral vitamin B12 is a safe and effective treatment for the B12 deficiency state. Even when intrinsic factor is not present to aid in the absorption of vitamin B12 (pernicious anemia) or in other diseases that affect the usual absorption sites in the terminal ileum, oral therapy remains effective.”

Full text, graphs, charts, illustrations and 20 references

http://www.aafp.org/afp/2003/0301/p979.html

Epidemiologic Reviews • July 2003

Diet and obstructive lung diseases

By I. Romieu and C. Trenga

Abstract

The results presented in this review suggest that the impact of nutrition on obstructive lung disease is most evident for antioxidant vitamins, particularly vitamin C and, to a lesser extent, vitamin E. By decreasing oxidant insults to the lung, antioxidants could modulate the development of chronic lung diseases and lung function decrement. Antioxidant vitamins could also play an important role in gene-environment interactions in complex lung diseases such as childhood asthma. Data also suggest that omega-3 fatty acids may have a potentially protective effect against airway hyperreactivity and lung function decrements; however, relevant data are still sparse. Although epidemiologic data suggest that consumption of fresh fruit may reduce risk of noncarcinogenic airway limitation, there are no clear data on which nutrients might be most relevant. While some studies evaluate daily intake of vitamin C, other studies use fruit consumption as a surrogate for antioxidant intake. Given the dietary intercorrelations among antioxidant vitamins, particularly vitamin C, beta-carotene, and flavonoids, as well as other micronutrients, it may be difficult to isolate a specific effect. Some population subgroups with higher levels of oxidative stress, such as cigarette smokers, may be more likely to benefit from dietary supplementation, since some studies have suggested that antioxidant intake may have a greater impact in this group. Studies of lung function decrement and COPD in adults suggest that daily intake of vitamin C at levels slightly exceeding the current Recommended Dietary Allowance (60 mg/day among nonsmokers and 100 mg/day among smokers) may have a protective effect (20). In the Schwartz and Weiss (85) and Britton et al. (87) studies, an increase of 40 mg/day in vitamin C intake led to an approximate 20-ml increase in FEV1. Daily mean vitamin C intakes in these studies were 66 mg and 99.2 mg, respectively, and the highest intake level (178 mg/day) was approximately three times the Recommended Dietary Allowance. Although the amplitude of the effect was modest, if these effects accumulate over 20-30 years, they could have a meaningful impact on the rate at which pulmonary function declines, particularly in symptomatic subjects (85). Longitudinal data support the hypothesis that fresh fruit consumption has a beneficial impact on the lung (95). Among children, consumption of fresh fruit, particularly fruit high in vitamin C, has been related to a lower prevalence of asthma symptoms and higher lung function (64). This effect was observed event at low levels of fruit consumption (one or two servings per week vs. less than one serving per week), which suggests that a small increase in dietary intake could have a beneficial effect. Consumption of fish has also been related to lower airway hyperreactivity among children (75) and higher lung function in adults (100); however, longitudinal data do not provide evidence that increased omega-3 fatty acid intake protects against lung disease (101). Experimental studies of persons with asthma suggest that magnesium infusion may have a place in the acute treatment of asthma, but it does not seem to have long-term benefits. The studies of sodium, selenium, and fish oils do not show convincing evidence of clinical benefits. Studies of vitamin C supplementation suggest a short-term protective effect on airway responsiveness and pulmonary function. It remains to be proven whether consistent use of vitamin C would have a protective effect on the evolution of chronic asthma. Results from supplementation studies conducted among subjects exposed to high levels of oxidants (57-60) suggest that daily intake of antioxidant vitamins exceeding the Recommended Dietary Allowance may have a beneficial effect on lung airways and that intake higher than the Recommended Dietary Allowance should be recommended for populations chronically exposed to photooxidant air pollutants (such as ozone), cigarette smoking, or vigorous exercise. It is difficult to determine the amounts of antioxidant vitamins that people should consume. In particular, although vitamin C was shown to have maximum bioavailability when given in a single dose of 200 mg (102), experiments on which this finding was based were conducted under normal conditions. Guidelines from the US National Cancer Institute (103) recommend consumption of five servings of fruit and vegetables daily, corresponding to a vitamin C intake exceeding 200 mg. Dietary surveys carried out in the US population indicate that less than 12 percent of US children and adults meet this recommended level of intake (104). Diet appears to be an important cofactor in the development of obstructive lung disease, although data are still sparse. There is a need for further research in experimental and epidemiologic settings to better understand the physiologic effects of antioxidant vitamins, omega-3 fatty acids, and other nutrients on lung tissues. The impact of diet on the incidence and evolution of asthma and COPD should be investigated using a cohort design that accounts for known risk factors. This will allow researchers to evaluate the exposure-disease relation over an adequate time frame and obtain insight into the causality of the relation. Some of these studies should enroll infants and young children to determine the impact of early diet on respiratory health. Research should also focus on the equally challenging policy issues--namely, finding effective methods of convincing people to increase their daily consumption of fresh fruits and vegetables, to stop smoking cigarettes, and to minimize their environmental and occupational exposure to pollutants and other agents that cause respiratory disease.

Full text, graphs, charts and 104 references

http://epirev.oxfordjournals.org/content/23/2/268.full.pdf

“Micronutrient deficiencies, also known as ‘hidden hunger’, are determining and aggravating factors for health status and quality of life. Three nutritional problems that have serious consequences are deficiencies of iron, vitamin A and iodine. It is estimated that in today’s world, iron deficiency anemia affects two billion people, mostly women and children. Blindness due to vitamin A deficiency affects 2.8 million children under 5 years of age. Iodine deficiency disorders affect 740 million people. Cuba is employing various programs to deal with these micronutrient deficiencies. Results of research carried out in Cuba have shown that vitamin A deficiency is nonexistent in children up to 7 y of age. Foods and preparations for these programs are delivered gratuitously or at very low prices.”

European Journal Of Clinical Nutrition • September 2003

Micronutrient deficiencies in developing and affluent countries

Author information

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Abstract

Micronutrient deficiencies, also known as ‘hidden hunger’, are determining and aggravating factors for health status and quality of life. Three nutritional problems that have serious consequences are deficiencies of iron, vitamin A and iodine. It is estimated that in today’s world, iron deficiency anemia affects two billion people, mostly women and children. Blindness due to vitamin A deficiency affects 2.8 million children under 5 years of age. Iodine deficiency disorders affect 740 million people. Cuba is employing various programs to deal with these micronutrient deficiencies. Dietary diversification, fortification of foods and supplementation with pharmaceutical preparations are included in Cuba’s response to these deficiencies. Urban agriculture is one strategy to increase dietary diversity. The aim is to increase both the availability and consumption of vegetables and fruits. Food fortification takes many forms in Cuba today and various supplementation programs are carried out. The most common supplemental program in the country is the prenatal program. This program provides four essential nutrients: iron, ascorbic acid, vitamin A and folic acid. At present, iodination covers more than 90% of the total amount of salt used for human consumption. Results of research carried out in Cuba have shown that vitamin A deficiency is nonexistent in children up to 7 y of age. Foods and preparations for these programs are delivered gratuitously or at very low prices.

http://www.ncbi.nlm.nih.gov/pubmed/12947458

L' Encephale • November 2003

Psychiatric manifestations of vitamin B12 deficiency: a case report

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Abstract

Psychiatric manifestations are frequently associated with pernicious anemia including depression, mania, psychosis, dementia. We report a case of a patient with vitamin B12 deficiency, who has presented severe depression with delusion and Capgras' syndrome, delusion with lability of mood and hypomania successively, during a period of two Months. Case report - Mme V., a 64-Year-old woman, was admitted to the hospital because of confusion. She had no history of psychiatric problems. She had history of diabetes, hypertension and femoral prosthesis. The red blood count revealed a normocytosis with anemia (hemoglobin=11,4 g/dl). At admission she was uncooperative, disoriented in time and presented memory and attention impairment and sleep disorders. She seemed sad and older than her real age. Facial expression and spontaneous movements were reduced, her speech and movements were very slow. She had depressed mood, guilt complex, incurability and devaluation impressions. She had a Capgras' syndrome and delusion of persecution. Her neurologic examination, cerebral scanner and EEG were postponed because of uncooperation. Further investigations confirmed anemia (hemoglobin=11,4 g/dl) and revealed vitamin B12 deficiency (52 pmol/l) and normal folate level. Antibodies to parietal cells were positive in the serum and antibodies to intrinsic factor were negative. An iron deficiency was associated (serum iron=7 micromol/l; serum ferritin concentration=24 mg/l; serum transferrin concentration=3,16 g/l). This association explained normocytocis anemia. Thyroid function, hepatic and renal tests, glycemia, TP, TCA, VS, VDRL-TPHA were normal. Vitamin B12 replacement therapy was started with hydroxycobalamin 1 000 ng/day im for 10 days and iron replacement therapy. Her mental state improved dramatically within a few days. After one week of treatment the only remaining symptoms were lability of mood, delusion of persecution, Capgras' syndrome but disappeared totally 9 days after the beginning of the treatment. A neurologic examination was possible because of cooperation. All the tendon reflexes of inferior members were absent. The plantars were in flexion and there was a left inferior member hypoesthesia. The cerebral scan and EEG were normal. Fundic biopsy, realized by fibroscopy, revealed fundic atrophia and intestinal metaplasia compatible with Biermers' disease. The iron deficiency exploration concluded diet deficiency. Mme V. appeared euphoric, her speech was very rapid with play on words and overactivity. This hypomania state totally disappeared 3 days after. Six Months after her hospitalisation, she presented an hypothyroidism (TSH=3,780; T3=1,35; T4=1,08). A thyroid hormones replacement was started and she continued to receive Monthly B12 replacement. Discussion: This case report illustrates psychiatric manifestations of Biermers' disease. The clinical arguments in favour are: white woman, more than 60 Years old, no history of psychiatric problems, atypical symptoms (confusional state with psychiatric symptoms), fluctuation of symptoms (severe depression with confusional state, delusion of persecution and Capgras' syndrome; delusion with lability of mood and hypomania), dramatic improvement after 9 days of vitamin B12 replacement therapy. The biological arguments are: anemia, vitamin B12 deficiency, normal folate level, atrophia and fundic metaplasia, positive antibodies to parietal cells in the serum, association between Biermers' disease and autoimmune disease (Haschimoto thyroidite). Psychiatric manifestations can occur in the presence of low serum B12 levels but in the absence of the other well recognized neurological and haematological abnormalities of pernicious anemia. Mental or psychological changes may precede haematological signs by Months or Years. They can be the initial symptoms or the only ones. Verbank et al. described the case of a patient with vitamin B12 deficiency in whom hypomania, paranoia and depression had been successively presented during a period of 5 Years before anemia have been developed. The case of Mme V. is similar in the succession of severe depression with delusion of persecution and Capgras' syndrome, delusion with lability of mood and hypomania, during a period of two Months. This report seems to be the first one of a sequence of several psychiatric states with pernicious anemia during a period of two Months with normocytosis anemia. To illustrate this illness we reviewed the literature regarding psychopathology associated with B12 deficiency. The most common psychiatric symptoms were depression, mania, psychotic symptoms, cognitive impairment and obsessive compulsive disorder. The neuropsychiatric severity by vitamin B12 deficiency and the therapeutic efficacy depends on the duration of signs and symptoms. Conclusion - We recommend consideration of B12 deficiency and serum B12 determinations in all the patients with organic mental disorders, atypical psychiatric symptoms and fluctuation of symptomatology. B12 levels should be evaluated with treatment resistant depressive disorders, dementia, psychosis or risk factors for malnutrition such as alcoholism or advancing age associated with neurological symptoms, anemia, malabsorption, gastrointestinal surgery, parasite infestation or strict vegetarian diet. In first intention, B12 deficiency should be researched by serum B12 determination (normal 200-950 pg/ml). Studies of methylmalonic acid and homocysteine showed that they are very sensitive functional indicators of cobalamin status especially when other evidence of cobalamin (B12) deficiency was equivocal. Measurement of methylmalonic acid (normal 73-271 nmol/l) and homocysteine (normal 5,4-13,9 micromol/l) should not replace the measurement of serum cobalamin.

http://www.ncbi.nlm.nih.gov/pubmed/15029091

Journal Of Nutrition • November 2003

Micronutrient deficiencies and cognitive functioning

Author information

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Abstract

“The relationship between four micronutrient deficiencies (iodine, iron, zinc and vitamin B-12) and children’s cognitive functioning is reviewed. Iodine deficiency during pregnancy has negative and irreversible effects on the developing fetus. Although there is some evidence that postnatal iodine deficiency is associated with cognitive deficits, the findings are controversial. Iron deficiency is widespread and has been associated to cognitive deficits, but the results of prevention trials are inconsistent. Zinc deficiency has been linked with low activity and depressed motor development among the most vulnerable children. Associations with cognitive development are less clear and may be limited to specific neuropsychological processes. Vitamin B-12 deficiency has been associated with cognitive problems among the elderly, but little is known about its effect on children’s cognitive functioning. Rates of vitamin B-12 deficiency are likely to be high because animal products are the only source of vitamin B-12. Although micronutrient deficiencies often co-occur in the context of poverty, little is known about the impact of multiple micronutrient deficiencies on cognitive development.”

Full text, graphs, charts and 58 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3140638/

“... the ageing of the European population will double the number of osteoporotic fractures over the next 50 years, unless adequate preventative measures are undertaken. The efficacy and safety of Ca(2+) and vitamin D supplements at preventing bone loss and reducing the risk of hip and other fractures have been assessed in different clinical trials, which are extensively discussed in this review.”

Pharmacology & Therapeutics • January 2002

Role of Ca(2+) and vitamin D in the prevention and treatment of osteoporosis

Author information

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Abstract

Osteoporosis is defined as a progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The clinical relevance of osteoporosis derives from the fractures that it produces. More than one-third of the adult women will suffer one or more osteoporotic fractures in their lifetime. The lifetime risk in men is approximately one-half that in women. The decrease of the bone mineral density is the most important cause of risk fracture. Among other factors, Ca(2+) and vitamin D deficiencies are important risk factors for a decrease in bone mineral density, consequently inducing osteoporosis. The high prevalence of vitamin D deficiency in healthy elderly people living mainly in southern European countries increase the risk of osteoporotic fractures in these populations above those anticipated for the general elderly population of the European community. In addition, the ageing of the European population will double the number of osteoporotic fractures over the next 50 years, unless adequate preventative measures are undertaken. The efficacy and safety of Ca(2+) and vitamin D supplements at preventing bone loss and reducing the risk of hip and other fractures have been assessed in different clinical trials, which are extensively discussed in this review.

http://www.ncbi.nlm.nih.gov/pubmed/11916540

Pediatrics • January 2002

Vitamin A supplements ameliorate the adverse effect of HIV-1, malaria, and diarrheal infections on child growth

Villamor E1, Mbise R, Spiegelman D, Hertzmark E, Fataki M, Peterson KE, Ndossi G, Fawzi WW.

OBJECTIVE

Evidence from animal experiments and observational studies in humans suggests that vitamin A plays a fundamental role in physical growth. However, results from vitamin A supplementation trials in children are inconsistent; whereas some did not find an overall effect on growth, others found benefits only among specific groups, including children with low concentrations of serum retinol or short duration of breast-feeding. The apparent lack of an overall effect of vitamin A on growth could be attributed to context-specific distribution of conditions that affect both growth and the response to supplementation, eg, baseline vitamin A status, deficiency of other nutrients (fat, zinc), and the presence of infectious diseases. Human immunodeficiency virus (HIV) infection, malaria, and diarrheal disease adversely affect growth and are associated with increased prevalence of vitamin A deficiency. We hypothesize that vitamin A supplementation could ameliorate the adverse effect of these infections on child growth.

METHODS

We conducted a randomized, clinical trial among 687 Tanzanian children who were 6 to 60 months of age and admitted to the hospital with pneumonia. Children were assigned to oral doses of 200 000 IU vitamin A (half that dose if <12 months) or placebo on the day of admission, a second dose on the following day, and third and fourth doses at 4 and 8 months after discharge from the hospital, respectively. Anthropometric measurements were obtained at baseline and at monthly visits to the study clinics during 12 months after the initial hospitalization. Surveillance on the incidence and severity of diarrhea and respiratory infections was conducted during biweekly visits, alternately at a study clinic and the child's home, using a pictorial diary that the mothers were trained to use. A blood specimen was drawn at baseline for determination of HIV status, malaria infection, and hemoglobin levels. We used mixed effects models to compare estimated total weight and height increases after 1 year of follow-up between treatment arms, overall and within levels of HIV status, malaria, and other possible baseline effect modifiers. We also assessed the potential modulating effect of vitamin A on the risk of stunting (height-for-age <-2 standard deviations of the gender-specific National Center for Health Statistics median reference) attributable to diarrheal and respiratory infections during follow-up, in the subset of children who were not stunted at baseline. A similar approach was followed for wasting (weight-for-height <-2 standard deviations of the reference median). Cox regression models were used to estimate relative risks and 95% confidence intervals (CI), treating episodes of infection as time-dependent covariates.

RESULTS

A total of 554 children had at least 2 follow-up measurements of height or weight and constituted the study base. Baseline characteristics did not differ significantly by treatment arm. Seventy-three percent of the children were <2 years of age, and 37% were <12 months; 31% were stunted at baseline and 9% were wasted. Malaria (Plasmodium falciparum) and HIV infection were found in 24% and 9% of the children, respectively. Median duration of follow-up was 351 days, with 10 measurements/child, on average, irrespectively of treatment assignment. Supplementation with vitamin A among children who had HIV infection and were <18 months of age resulted in a significant length increase. Four months after the first dose, infants who were HIV positive in the vitamin A arm had gained, on average, 2.8 cm (95% CI: 1.0-4.6) more than children who received placebo, whereas no effect was observed among infants who were HIV negative (difference at 4 months: -0.2 cm; 95% CI: -0.8-0.5). Children who were <12 months of age and had malaria at enrollment experienced a 747-g (95% CI: 71-1423) higher yearly weight gain attributable to vitamin A; among children without malaria, however, the supplements did not have a significant effect (-57 g; 95% CI: -461-348). These results remained unchanged after controlling for indicators of the socioeconomic and nutritional status at baseline. Linear growth was also improved by vitamin A among children from households with poor water supply (0.8 cm/year; 95% CI: 0-1.5) but not in children with tap water in the house or compound (-1.0 cm/year; 95% CI: -1.9-0). Weight gain was greater among children with mid-upper arm circumference below the 25th percentile of the age-specific distribution at baseline (458 g/year; 95% CI: 1-905), but no benefit was evident among children with higher mid-upper arm circumference. The risk of stunting associated with episodes of persistent diarrhea (lasting 14 or more days) during follow-up was virtually eliminated by vitamin A supplements. Among children in the placebo group, the average risk of stunting associated with 1 or more episodes of persistent diarrhea between 2 consecutive visits was 5.2 times higher (95% CI: 2.4-11.2) than that of children without diarrhea or with acute episodes. In contrast, among children who received vitamin A, there was virtually no risk of stunting associated with persistent diarrhea (relative risk: 1.0; 95% CI: 0.3-1.3). This effect was slightly attenuated after controlling for the number of household possessions, gender, baseline low arm circumference, HIV infection, and presence of malaria parasites in blood. Vitamin A supplements did not modify the associations between respiratory infections and the risk of stunting or wasting.

CONCLUSIONS

Vitamin A supplementation improves linear and ponderal growth in infants who are infected with HIV and malaria, respectively, and decreases the risk of stunting associated with persistent diarrhea. Supplementation could constitute a low-cost, effective intervention to decrease the burden of growth retardation in settings where infectious diseases are highly prevalent.

http://www.ncbi.nlm.nih.gov/pubmed/11773574

“... sunlight exposure or the ultraviolet irradiation are limited by concern about skin cancer and skin disease. The most rational approach to reducing vitamin D insufficiency is supplementation. In Europe, the RDA is 400-800 IU (10-20 microg) daily for people aged 65 years or over. This dose is safe and free of side effects. In conclusion, in Europe a low calcium intake and a suboptimal vitamin D status are very common in the elderly. Evidence supports routine supplementation for these people at risk of osteoporosis, by providing a daily intake of 700-800 mg of calcium and 400-800 IU of vitamin D. This is an effective, safe and cheap means of preventing osteoporotic fractures.”

Public Health And Nutrition • April 2001

Calcium and vitamin D nutrition and bone disease of the elderly

Author information
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Abstract

Osteoporosis, a systemic skeletal disease characterized by a low bone mass, is a major public health problem in EC member states because of the high incidence of fragility fractures, especially hip and vertebral fracture. In EC member states the high incidence of osteoporotic fractures leads to considerable mortality, morbidity, reduced mobility and decreased quality of life. In 1995 the number of hip fractures in 15 countries of EC has been 382,000 and the estimated total care cost of about 9 billion of ECUs. Given the magnitude of the problem public health measures are important for preventive intervention. Skeletal bone mass is determined by a combination of endogenous (genetic, hormonal) and exogenous (nutritional, physical activity) factors. Nutrition plays an important role in bone health. The two nutrients essential for bone health are calcium and vitamin D. Reduced supplies of calcium are associated with a reduced bone mass and osteoporosis, whereas a chronic and severe vitamin D deficiency leads to osteomalacia, a metabolic bone disease characterized by a decreased mineralization of bone. Vitamin D insufficiency, the preclinical phase of vitamin D deficiency, is most commonly found in the elderly. The major causes of vitamin D deficiency and insufficiency are decreased renal hydroxylation of vitamin D, poor nutrition, scarce exposition to sunlight and a decline in the synthesis of vitamin D in the skin. The daily average calcium intake in Europe has been evaluated in the SENECA study concerning the diet of elderly people from 19 towns of 10 European countries. In about one third of subjects the dietary calcium intake results were very low, between 300 and 600 mg/day in women, and 350 and 700 mg/day in men. Calcium supplements reduce the rate of bone loss in osteoporotic patients. Some recent studies have reported a significant positive effect of calcium treatment not only on bone mass but also on fracture incidence. The SENECA study, has also shown that vitamin D insufficiency is frequent in elderly populations in Europe. There are a number of studies on the effects of vitamin D supplementation on bone loss in the elderly, showing that supplementations with daily doses of 400-800 IU of vitamin D, given alone or in combination with calcium, are able to reverse vitamin D insufficiency, to prevent bone loss and to improve bone density in the elderly. In recent years, there has been much uncertainty about the intake of calcium for various ages and physiological states. In 1998, the expert committee of the European Community in the Report on Osteoporosis-Action on prevention, has given the recommended daily dietary allowances (RDA) for calcium at all stage of life. For the elderly population, above age 65 the RDA is 700-800 mg/day. The main source of calcium in the diet are dairy products (milk, yoghurts and cheese) fish (sardines with bones), few vegetables and fruits. The optimal way to achieve adequate calcium intake is through the diet. However, when dietary sources are scarce or not well tolerated, calcium supplementation may be used. Calcium is generally well tolerated and reports of significant side-effects are rare. Adequate sunlight exposure may prevent and cure vitamin D insufficiency. However, the sunlight exposure or the ultraviolet irradiation are limited by concern about skin cancer and skin disease. The most rational approach to reducing vitamin D insufficiency is supplementation. In Europe, the RDA is 400-800 IU (10-20 microg) daily for people aged 65 years or over. This dose is safe and free of side effects. In conclusion, in Europe a low calcium intake and a suboptimal vitamin D status are very common in the elderly. Evidence supports routine supplementation for these people at risk of osteoporosis, by providing a daily intake of 700-800 mg of calcium and 400-800 IU of vitamin D. This is an effective, safe and cheap means of preventing osteoporotic fractures.

http://www.ncbi.nlm.nih.gov/pubmed/11683549

Proceedings For The Society For Experimental Biology And Medicine • March 2000

Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence?

Author information

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Abstract

“The environment in which the encounter of antigen with the immune system occurs determines whether tolerance, infectious immunity, or autoimmunity results. Geographical areas with low supplies of vitamin D (for example Scandinavia) correlate with regions with high incidences of multiple sclerosis, arthritis, and diabetes. The active form of vitamin D has been shown to suppress the development of autoimmunity in experimental animal models. Furthermore, vitamin D deficiency increases the severity of at least experimental autoimmune encephalomyelitis (mouse multiple sclerosis). Targets for vitamin D in the immune system have been identified, and the mechanisms of vitamin D-mediated immunoregulation are beginning to be understood. This review discusses the possibility that vitamin D status is an environmental factor, which by shaping the immune system affects the prevalence rate for autoimmune diseases such as multiple sclerosis, arthritis, and juvenile diabetes.”

http://www.ncbi.nlm.nih.gov/pubmed/10719834

American Journal Of Clinical Nutrition • June 1999

Effect of iron-, iodine-, and beta-carotene-fortified biscuits on the micronutrient status of primary school children: a randomized controlled trial

Author information

van Stuijvenberg ME1, Kvalsvig JD, Faber M, Kruger M, Kenoyer DG, Benadé AJ.

Abstract

BACKGROUND

Deficiencies of iron, iodine, and vitamin A are prevalent worldwide and can affect the mental development and learning ability of schoolchildren.

OBJECTIVE

The aim of this study was to determine the effect of micronutrient-fortified biscuits on the micronutrient status of primary school children.

DESIGN

Micronutrient status was assessed in 115 children aged 6-11 y before and after consumption of biscuits (fortified with iron, iodine, and beta-carotene) for 43 wk over a 12-mo period and was compared with that in a control group (n = 113) who consumed nonfortified biscuits. Cognitive function, growth, and morbidity were assessed as secondary outcomes.

RESULTS

There was a significant between-group treatment effect on serum retinol, serum ferritin, serum iron, transferrin saturation, and urinary iodine ($P < 0.0001$) and in hemoglobin and hematocrit ($P < 0.05$). The prevalence of low serum retinol concentrations (<0.70 micromol/L) decreased from 39.1% to 12.2%, of low serum ferritin concentrations (<20 microg/L) from 27.8% to 13.9%, of anemia (hemoglobin <120 g/L) from 29.6% to 15.6%, and of low urinary iodine concentrations (<100 microg/L) from 97.5% to 5.4%. There was a significant between-group treatment effect ($P < 0.05$) in cognitive function with the digit span forward task (short-term memory). Fewer school days were missed in the intervention than in the control group because of respiratory- ($P = 0.097$) and diarrhea-related ($P = 0.013$) illnesses. The intervention had no effect on anthropometric status [corrected].

CONCLUSIONS

Fortified biscuits resulted in a significant improvement in the micronutrient status of primary school children from a poor rural community and also appeared to have a favorable effect on morbidity and cognitive function.

http://www.ncbi.nlm.nih.gov/pubmed/10075336

“Fortified biscuits resulted in a significant improvement in the micronutrient status of primary school children from a poor rural community and also appeared to have a favorable effect on morbidity and cognitive function.”

“Cobalamin (vitamin B12) deficiency is more common in the elderly than in younger patients. This is because of the increased prevalence of cobalamin malabsorption in this age group, which is mainly caused by (autoimmune) atrophic body gastritis. Cobalamin supplementation is affordable and nontoxic, and it may prevent irreversible neurological damage if started early. Elderly individuals with cobalamin deficiency may present with neuropsychiatric or metabolic deficiencies, without frank macrocytic anaemia.”

Drugs And Aging • April 1998

Age-related changes in cobalamin (vitamin B12) handling. Implications for therapy

Author information
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Abstract

Cobalamin (vitamin B12) deficiency is more common in the elderly than in younger patients. This is because of the increased prevalence of cobalamin malabsorption in this age group, which is mainly caused by (autoimmune) atrophic body gastritis. Cobalamin supplementation is affordable and nontoxic, and it may prevent irreversible neurological damage if started early. Elderly individuals with cobalamin deficiency may present with neuropsychiatric or metabolic deficiencies, without frank macrocytic anaemia. An investigation of symptoms and/or signs includes the diagnosis of deficiency as well as any underlying cause. Deficiency states can still exist even when serum cobalamin levels are higher than the traditional lower reference limit. Cobalamin-responsive elevations of serum methylmalonic acid (MMA) and homocysteine are helpful laboratory tools for the diagnosis. The health-related reference ranges for homocysteine and MMA appear to vary with age and gender. Atrophic body gastritis is indirectly diagnosed by measuring serum levels of gastrin and pepsinogens, and it may cause dietary cobalamin malabsorption despite a normal traditional Schilling’s test. The use of gastroscopy may also be considered to diagnose dysplasia, bacterial overgrowth and intestinal villous atrophy in healthy patients with atrophic body gastritis or concomitant iron or folic acid deficiency. Elderly patients respond to cobalamin treatment as fully as younger patients, with complete haematological recovery and complete or good partial resolution of neurological deficits. Chronic dementia responds poorly but should, nevertheless, be treated if there is a metabolic deficiency (as indicated by elevated homocysteine and/or MMA levels). Patients who are at risk from cobalamin deficiency include those with a gastrointestinal predisposition (e.g. atrophic body gastritis or previous partial gastrectomy), autoimmune disorders [type 1 (insulin-dependent) diabetes mellitus and thyroid disorders], those receiving long term therapy with gastric acid inhibitors or biguanides, and those undergoing nitrous oxide anaesthesia. To date, inadequate cobalamin intake has not proven to be a major risk factor. Intervention trials of cobalamin, folic acid and pyridoxine (vitamin B6) in unselected elderly populations are currently under way.

http://www.ncbi.nlm.nih.gov/pubmed/9571392

“... we evaluated patients with severe congestive heart failure to determine the prevalence of osteoporosis and to characterize relationships between mineral homeostasis, bone turnover, bone mass, and severity of congestive heart failure.”

The American Journal of Medicine • September 1997

Bone Mass, Vitamin D Deficiency, and Hyperparathyroidism in Congestive Heart Failure

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Abstract

PURPOSE

In contrast to renal and hepatic failure, congestive heart failure (CHF) has not been associated with a defined metabolic bone disorder. However, low bone mass has been reported in patients with CHF who receive a cardiac transplant. Both the pathophysiology and therapy of CHF may influence bone and mineral homeostasis and evidence that calciotropic hormones may affect cardiovascular function is accumulating. Therefore, we evaluated patients with severe CHF to determine the prevalence of osteoporosis and to characterize relationships between mineral homeostasis, bone turnover, bone mass, and severity of CHF.

PATIENTS AND METHODS

One hundred one patients (79 men and 22 women, aged 25 to 70 years) with severe CHF (New York Heart Association functional class III or IV) referred for consideration for cardiac transplantation were evaluated with measurements of serum 25-hydroxyvitamin D (25-OHD), 1,25 dihydroxyvitamin D [1,25(OH)2D], intact parathyroid hormone (PTH), markers of bone turnover (serum osteocalcin, urinary hydroxyproline, and pyridinium crosslinks); bone mineral density (BMD) by dual energy x-ray absorptiometry was measured in 91 patients. Left ventricular ejection fraction (LVEF) and resting cardiac output (CO) were determined in 88 and maximal treadmill exercise testing and peak oxygen consumption were performed in 45 patients.

RESULTS

Osteoporosis (T score ≤-2.5) was present in 7% at the lumbar spine, 6% at the total hip, and 19% at the femoral neck. Osteopenia (T scores between -1.0 and -2.5) was present in 43% at the lumbar spine, 47% at the total hip, and 42% at the femoral neck. Women were more severely affected (P = 0.007). Frankly low serum 25-OHD (≤9 pg/mL) and 1,25(OH)2D (≤15 pg/mL) levels were found in 17% and 26% of the patients, respectively, and elevated serum PTH (≥65 pg/mL) in 30%. Both low serum 1,25(OH)2D and increased serum PTH were associated with prerenal azotemia. Low serum vitamin D metabolites were associated with biochemical evidence of increased bone turnover, but BMD did not differ by vitamin D or PTH status. Patients with more severe CHF had significantly lower vitamin D metabolites and higher bone turnover, whereas elevated PTH was associated with better LVEF (21 ± 1 versus 18 ± 1%; P = 0.05) and correlated positively with resting CO (R = 0.220; P = 0.04).

CONCLUSIONS

Osteopenia or osteoporosis were observed in approximately half of these patients with severe CHF. Abnormal calciotropic hormone concentrations, also common, were associated with evidence of increased bone resorption but were not related to BMD in this cross-sectional study. Abnormal concentrations of calciotropic hormones were related to the severity of cardiovascular compromise. Because both low BMD and low serum concentrations of 25-OHD in patients with CHF are associated with higher rates of bone loss and fracture after cardiac transplantation, patients should be evaluated for and receive appropriate therapy for these disorders.

http://www.sciencedirect.com/science/article/pii/S0002934397001423

Nutrition Reviews • December 1996

Folate, vitamin B12, and neuropsychiatric disorders

Author information

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Abstract

“Folate and vitamin B12 are required both in the methylation of homocysteine to methionine and in the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B12 deficiency may cause similar neurologic and psychiatric disturbances including depression, dementia, and a demyelinating myelopathy. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatry of these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurologic and psychiatric disturbances that are associated with folate and vitamin B12 deficiency.”

http://www.ncbi.nlm.nih.gov/pubmed/9155210

Gastroenterologist • December 1995

Vitamin B12 in health and disease: part I—inherited disorders of function, absorption, and transport

Author information

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Abstract

All of vitamin B12 in nature is of microbial origin. Cobalamin, as vitamin B12 should correctly be termed, is a large polar molecule that must be bound to specialized transport proteins to gain entry into cells. Entry from the lumen of the intestine under physiological conditions occurs only in the ileum and only when bound to intrinsic factor. It is transported into all other cells only when bound to another transport protein, transcobalamin II. Congenital absence or defective synthesis of intrinsic factor or transcobalamin II result in megaloblastic anemia. The Immerslund-Graesbeck syndrome, a congenital defect in the transcellular transport of cobalamin through the ileal cell during absorption, also presents with megaloblastic anemia, but with accompanying albuminuria. In most bacteria and in all mammals, cobalamin regulates DNA synthesis indirectly through its effect on a step in folate metabolism, the conversion of N5-methyltetrahydrofolate to tetrahydrofolate, which in turn is linked to the conversion of homocysteine to methionine. This reaction occurs in the cytoplasm, and it is catalyzed by methionine synthase, which requires methyl cobalamin (MeCbl), one of the two coenzyme forms of the vitamin, as a cofactor. Defects in the generation of MeCbl (cobalamin E and G diseases) result in homocystinuria; affected infants present with megaloblastic anemia, retardation, and neurological and ocular defects. 5'-Deoxyadenosyl cobalamin (AdoCbl), the other coenzyme form of cobalamin, is present within mitochondria, and it is an essential cofactor for the enzyme Methylmalonyl-CoA mutase, which converts L-methylmalonyl CoA to succinyl CoA. This reaction is in the pathway for the metabolism of odd chain fatty acids via propionic acid, as well as that of the amino acids isoleucine, methionine, threonine, and valine. Impaired synthesis of AdoCbl (cobalamin A or B disease) results in infants with methylmalonic aciduria who are mentally retarded, hypotonic, and who present with metabolic acidosis, hypoglycemia, ketonemia, hyperglycinemia, and hyperammonemia. Megaloblastic anemia does not develop in these children because adequate amounts of MeCbl are present, but the effect of methylmalonic acid on marrow stem cells may give rise to pancytopenia. Congenital absence of reductases in the cytoplasm, which normally reduce the cobalt atom in cobalamin from its oxidized to its reduced state (cobalamin C and D diseases), results in impaired synthesis of both MeCbl and AdoCbl. Both methylmalonic aciduria and homocystinuria therefore develop in these children, and they present with megaloblastosis, mental retardation, a host of neurological and ocular disorders, and failure to thrive; however, they do not have hyperglycinemia or hyperammonemia. A similar biochemical profile and clinical presentation is also seen in cobalamin F disease, which results from a defect in the release of cobalamin from lysosomes, following receptor-mediated endocytosis of the transcobalamin II-cobalamin complex into cells. It is important to recognize these inborn errors of cobalamin absorption, transport, or function as soon after birth as possible, because most respond (in some patients more fully than others) to parenteral administration of cobalamin. Delays in diagnosis can lead to grave clinical consequences.

http://www.ncbi.nlm.nih.gov/pubmed/8775094

American Journal Of Gastroenterology • June 1994

The contribution of vitamin K2 (menaquinones) produced by the intestinal microflora to human nutritional requirements for vitamin K

Author information

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Abstract

BACKGROUND

Coagulopathy manifest by elevation of the prothrombin time (PT) in patients receiving broad spectrum antimicrobials indirectly suggests a role for intestinal microflora synthesized menaquinone (MK) in the maintenance of normal coagulation. Nonetheless, no direct evidence is available to support this contention.

OBJECTIVE

Our objective was therefore to provide evidence that bacterially produced MK may be absorbed by the distal small bowel of humans.

METHODS

Using a cell harvester, Staphylococcus aureus (ATCC 29213) was grown in 12-L batches, harvested, and extracted by high performance liquid chromatography (HPLC) to obtain 8 mg of pure MK. Four normal volunteers were placed on a diet severely restricted in vitamin K1 (median 32-40 U/day), and were given warfarin to maintain an International Normalized Ratio of approximately 2.0. On the 10th day of warfarin administration, naso-ileal intubation was performed and 1.5 mg of MK was delivered into the ileum. PT, factor VII, II and serum vitamin K1 levels were monitored throughout the study.

RESULTS

Mean serum vitamin K1 levels were reduced to 30% of the pre-diet value at the time of MK administration. Within 24 h of ileal MK administration, there was a significant ($p < 0.05$) increase in the factor VII level of 0.28 +/- 0.10 U/ml (mean +/- SEM) and a significant decrease of 2.5 (+/- 0.1) s in the PT, whereas in the control phase (during which no MK was administered), there were no significant changes in the PT or factor VII at corresponding time intervals.

CONCLUSION

These data provide direct evidence for the absorption of vitamin K2 from the distal small bowel, supporting a definite role for bacterially synthesized vitamin K2 in contributing to the human nutritional requirements of this vitamin.

http://www.ncbi.nlm.nih.gov/pubmed/8198105

National Institutes Of Health Consensus Statement • June 1994

Optimal calcium intake

Abstract

"The National Institutes of Health Consensus Development Conference on Optimal Calcium Intake brought together experts from many different fields including osteoporosis and bone and dental health, nursing, dietetics, epidemiology, endocrinology, gastroenterology, nephrology, rheumatology, oncology, hypertension, nutrition and public education, and biostatistics, as well as the public, to address the following questions: (1) What is the optimal amount of calcium intake? (2) What are the important cofactors for achieving optimal calcium intake? (3) What are the risks associated with increased levels of calcium intake? (4) What are the best ways to attain optimal calcium intake? (5) What public health strategies are available and needed to implement optimal calcium intake recommendations? and (6) What are the recommendations for future research on calcium intake? The consensus panel concluded that: A large percentage of Americans fail to meet currently recommended guidelines for optimal calcium intake. On the basis of the most current information available, optimal calcium intake is estimated to be 400 mg/day (birth-6 months) to 600 mg/day (6-12 months) in infants; 800 mg/day in young children (1-5 years) and 800-1,200 mg/day for older children (6-10 years); 1,200-1,500 mg/day for adolescents and young adults (11-24 years); 1,000 mg/day for women between 25 and 50 years; 1,200-1,500 mg/day for pregnant or lactating women; and 1,000 mg/day for postmenopausal women on estrogen replacement therapy and 1,500 mg/day for postmenopausal women not on estrogen therapy. Recommended daily intake for men is 1,000 mg/day (25-65 years). For all women and men over 65, daily intake is recommended to be 1,500 mg/day, although further research is needed for this age group. These guidelines are based on calcium from the diet plus any calcium taken in supplemental form. Adequate vitamin D is essential for optimal calcium absorption. Dietary constituents, hormones, drugs, age, and genetic factors influence the amount of calcium required for optimal skeletal health. Calcium intake, up to a total intake of 2,000 mg/day, appears to be safe in most individuals. The preferred source of calcium is through calcium-rich foods such as dairy products. Calcium-fortified foods and calcium supplements are other means by which optimal calcium intake can be reached in those who cannot meet this need by ingesting conventional foods. A unified public health strategy is needed to ensure optimal calcium intake in the American population."

http://www.ncbi.nlm.nih.gov/pubmed/7599655

American Journal Of Clinical Nutrition • June 1992

Nutritional factors in physical and cognitive functions of elderly people

Author information

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Abstract

"The quality of life of aging individuals depends profoundly on their capacity for physical mobility, mental alertness, and cognitive function. Independence and self-esteem are strongly determined by physical and mental capacities. Stimulated by reports of declining function with age, investigators have examined the relationships between lifestyle factors and maintenance of functional status. Growing evidence supports the view that continued physical activity and good nutritional status are important determinants of physical and cognitive function. It is possible that some of the decline in cognitive function associated with aging is preventable or reversible with improved vitamin nutriture, especially vitamin B-12, vitamin B-6, and folate. It might well be argued that the most practical outcome of research on the relationship of diet and nutrition to the aging process would be a better understanding of the ways in which our behavior can maintain a vigorous quality of life."

http://www.ncbi.nlm.nih.gov/pubmed/1590263

Progress In Food Nutrition Science • October 1992

The production of menaquinones (vitamin K2) by intestinal bacteria and their role in maintaining coagulation homeostasis

Author information

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Abstract

“Vitamin K is an essential cofactor necessary for the production of clotting factors II, VII, IX, and X in humans and has recently been found to be an essential factor for many other proteins in the body. There are two sources of this essential vitamin, including vitamin K1, or phylloquinone which is primarily found in green leafy vegetables and vitamin K2 or menaquinone which is synthesized by certain intestinal bacteria. The precise contribution of the bacterially synthesized menaquinone to overall vitamin K requirements in man is unknown. This paper reviews the available literature regarding the production and liberation of menaquinones from bacteria, the animal experiments which have been done to examine the absorption of menaquinones and the indirect and direct evidence in humans regarding utilization of menaquinones. The preponderance of the evidence suggests that bacterially synthesized menaquinones, particularly in the ileum can and do play a significant role in contributing to vitamin K requirements in humans to prevent clinically significant coagulopathy, especially during periods of episodic dietary lack of the vitamin.”

http://www.ncbi.nlm.nih.gov/pubmed/1492156

Cell Calcium • December 1988

Involvement of 1,25-dihydroxyvitamin D3 in regulating myocardial calcium metabolism: Physiological and pathological actions

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Abstract

The role of the prohormone vitamin D3 in regulating calcium and phosphate metabolism in the intestine, kidney, and bone has been known for several decades [1]. Recent studies have provided evidence that vitamin D3, may also play an important role in regulating metabolism in other organs, including heart [2]. This role has been suggested by the identification of a specific receptor for 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], the active metabolite of vitamin D3, in these tissues [3–5], as well as the presence of a 1.25(OH)2D3-dependent calcium binding protein [6, 7].

“Although administration of excessive quantities of vitamin D3 has been shown in many studies to produce myocardial calcinosis and heart failure [8, 9], the importance of vitamin D3 in regulating myocardial metabolism under normal conditions has only recently been demonstrated [10, 11]. The purpose of the present review is to assess the current status of research regarding the pathological and physiological actions of vitamin D3 on the heart. The initial section of this report will focus on the pathological effects of excessive vitamin D3 on cardiovascular function, while the latter sections will describe recent studies related to the involvement of 1,25(OH)2D3 in regulating calcium homeostasis in ventricular cells and the relationship between vitamin D3 and myocardial contractility.”

Full text with references

http://www.sciencedirect.com/science/article/pii/0143416088900097

CRC Critical Reviews Of Food Science And Nutrition • July 1980

Determination of vitamin K in foods: a review

By D.B. Parrish

Abstract

"Vitamin K receives less dietary attention and fewer assays in foods than other fat-soluble vitamins. It is widely distributed in foods, usually at low concentrations. The human requirement is small. Intestinal bacteria synthesize vitamin K, which presumably helps provide the metabolic requirements for vitamin K. An RDA for vitamin K has not been published, but infants fed milk-substitute formulas risk vitamin K deficiency and it is recommended that those formulas contain supplemental vitamin K. Vitamin K in foods includes phylloquinone (K1) found in plants and several menaquinones (K2) found in animals and synthesized by microorganisms. Many vitamin K methods were developed primarily to identify forms present and determine their relative bioactivities. Until recently bioassays with chicks were the only practical methods to determine vitamin K content of foods. Various physicochemical methods have been developed to determine vitamins K in pure solutions, concentrates, and pharmaceuticals. Because of low concentrations of vitamin K in foods and the extensive purifications of extracts required, there has been only limited use of physicochemical methods, such as column chromatography, thin-layer chromatography, and high-performance liquid chromatography, with foods; the latter method perhaps offers the greatest possibilities for further development."

http://www.ncbi.nlm.nih.gov/pubmed/7002471

CRC Critical Reviews Of Food Science And Nutrition • November 1979

Determination of vitamin D in foods: a review

by D.B. Parrish

Abstract

“Determining vitamin D content in foods is difficult because in natural foods of highest vitamin D activity, and even in vitamin D-fortified foods, only small quantities are present, and many other compounds are extracted along with vitamin D that cause difficulties in purifying the extract or in the spectrophotometry or colorimetry that follows. Several physicochemical methods--such as spectrophotometric, colorimetric, thin-layer chromatographic, adsorption, partition, gas-liquid, and high-performance column chromatographic--have been tried for assay foods for vitamin D, but none of them have been accepted for official or routine use; they are time consuming and expensive, or lack the required sensitivity, precision, or accuracy. Curative biological assays, based on degree of healing of a leg bone of rats previously made rachitic, is the generally accepted method to determine vitamin D content of foods. However, that method also requires too much time and is expensive. The recently developed high-performance liquid chromatographic method may offer the most for establishing a satisfactory physicochemical method for determining vitamin D in foods. Many of the difficulties and problems in assaying foods for vitamin D are discussed.”

http://www.ncbi.nlm.nih.gov/pubmed/389562

CRC Critical Reviews Of Food Science And Nutrition • May 1977

Determination of vitamin A in foods—a review

By D.B. Parrish

Abstract

“Formerly, few foods were routinely analyzed for vitamin A, but recent emphasis on nutrient requirements, nutrient labeling, and use of dietary convenience foods has created need for determining vitamin A in a variety of foods. There are many vitamin A methods--some suitable for certain products only. For regulatory purposes, the FDA specifies the AOAC method where it is applicable. However, some food analysts and organizations continue with their own vitamin A methods. If possible, a single, widely applicable general method should be used for vitamin A in foods. Vitamin A may be determined by spectrophotometric, colorimetric, and fluorometric procedures. Sometimes chromatography is required as an important part of the method. Colorimetric procedures with SbCl3 are now most widely used to measure vitamin A (retinol) in foods. If vitamin A content is high enough and extracts sufficiently free of interfering substances, spectrophotometric or flurometric methods are satisfactory. Methods in various stages of development for determining vitamin A in foods are based on flurospectrophotometry, gas-liquid chromatography, high-performance liquid chromatography, and automation. To estimate total vitamin A nutritional value of certain foods may also require determination of vitamin A isomerization and contents of carotenes, cryptoxanthin, reinaldehyde, and apo-carotenal.”

http://www.ncbi.nlm.nih.gov/pubmed/336289

CHAPTER FORTY

Brazzein - Cweet

The Peer Review

Brazzein is a sweet-tasting protein extracted from the West African fruit of the climbing plant Oubli. It was first isolated as an enzyme by the University of Wisconsin–Madison in 1994.

Brazzein is found in the extracellular region, in the pulp tissue surrounding the seeds. With pentadin, discovered in 1989, brazzein is the second sweet-tasting protein discovered in the Oubli fruit. Like the other sweet proteins discovered in plants, such as monellin and thaumatin, it is extremely sweet compared to commonly used sweeteners (500 to 2000 times sweeter than sucrose).

TRADITIONAL USES

The Oubli plant (from which the protein was isolated) grows in Gabon and Cameroon, where its fruit has been consumed by the apes and local people for a long time. Due to brazzein and pentadin, the berries of the plant are incredibly sweet. African locals call them "Oubli" (French for "forgot") in their vernacular language because their taste is said to encourage nursing infants to forget their mother's milk, as once they eat them they are said to forget to come back to the village to see their mother.

SWEETNESS AND AS A SWEETENER

On a weight basis, brazzein is 500 to 2000 times sweeter than sucrose, compared to 10% sucrose and 2% sucrose solution respectively. Its sweet perception is more similar to sucrose than that of thaumatin, with a clean sweet taste, lingering aftertaste, and slight delay (longer than aspartame) in an equi-sweet solution. Brazzein is stable over a broad pH range from 2.5 to 8 and heat stable at 98°C for 2 hours. Brazzein represents an alternative to available low-calorie sweeteners. As a protein, it is safe for diabetics. It is also very soluble in water. When blended with other sweeteners, such as aspartame and stevia, brazzein reduces side aftertaste and complements their flavor. Its taste profile is closer to sucrose than other natural sweeteners (apart from thaumatin). Unlike other sweet-tasting proteins, it can withstand heat, making it more suitable for industrial food processing. Increasing interest in brazzein makes it difficult to source naturally from Gabon, but it can also be synthesised by a solid-phase method. Recombinant proteins were successfully produced via E. coli.

The Texas companies Prodigene and Nectar Worldwide were among the licensees to use Wisconsin Alumni Research Foundation patents on brazzein, and genetically engineer the enzyme into maize. Brazzein then can be commercially extracted from the maize through ordinary milling. Approximately one ton of maize yields 1-2 kilograms of brazzein. It can also be engineered into plants like wheat to make pre-sweetened grains, e.g. for cereals.

'Natur Research Ingredients' planned to market brazzein under the Cweet (1000x) and (3000x) brands by 2009 and has developed a web site although Brazzein is still not sold in the US.

PATENT CONTROVERSY

Despite the fact that the sweet taste of the berries was well known in West Africa, the University of Wisconsin claims that the sweet compound (brazzein) is its own invention and admit to no connection with the country of Gabon. This fact, which involved appropriation of legal rights by means of patents over indigenous biomedical knowledge without compensation to the indigenous groups, is considered an act of Biopiracy by GRAIN and Green Peace.

“Brazzein (Brz) is a small (54 amino acid residue) sweet tasting protein with physical and taste properties superior to other non-carbohydrate sweeteners.”

Protein Science • March 2016

Structure-function relationships of brazzein variants with altered interactions with the human sweet taste receptor

Author information

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Abstract

Brazzein (Brz) is a small (54 amino acid residue) sweet tasting protein with physical and taste properties superior to other non-carbohydrate sweeteners. In an investigation of sequence-dependent functional properties of the protein, we used NMR spectroscopy to determine the three-dimensional structures and dynamic properties of two Brz variants: one with a single-site substitution (D40K), which is three-fold sweeter than wild-type Brz, and one with a two-residue insertion between residues 18 and 19 (ins18 RI19), which is devoid of sweetness. Although the three-dimensional folds of the two variants were very similar to wild-type Brz, they exhibited local conformational and dynamic differences. The D40K substitution abolished the strong inter-stand H-bond between the side chains of residues Gln46 and Asp40 present in wild-type Brz and increased the flexibility of the protein especially at the mutation site. This increased flexibility presumably allows this site to interact more strongly with the G-protein coupled human sweet receptor. On the other hand, the Arg-Ile insertion within Loop9-19 leads to distortion of this loop and stiffening of the adjacent site whose flexibility appears to be required for productive interaction with the sweet receptor.

http://www.ncbi.nlm.nih.gov/pubmed/26701738

Journal Of Science, Food And Agriculture • July 2016

Importance of Glu53 in the C-terminal region of brazzein, a sweet-tasting protein

Author information

Lim JK1, Jang JC1, Kong JN1, Kim MC1, Kong KH1.

Abstract

BACKGROUND

The sweetness of brazzein, one of the known sweet proteins, is dependent on charges and/or structures of its specific amino acid side chains. As the residues in the C-terminus of brazzein are known to play a critical role in sweetness, the currently unknown function of Glu53 requires further study.

RESULTS

To identify important residues responsible for the sweetness of the protein brazzein, four mutants of the Glu53 residue in the C-terminal region of des-pE1M-brazzein, which lacks the N-terminal pyroglutamate, were constructed using site-directed mutagenesis. Mutations of Glu53 substitution to Ala or Asp significantly decreased the sweetness. On the other hand, a Lys mutation resulted in a molecule with sweetness similar to that of des-pE1M-brazzein. Mutation of Glu53 to Arg resulted in a molecule significantly sweeter than des-pE1M-brazzein, which agrees with previous findings showing that mutation with positively charged residues results in a sweeter protein.

CONCLUSION

Our results suggest that the residue at position 53 is crucial for the sweetness of brazzein, which may be interacting with the sweet-taste receptor.

http://www.ncbi.nlm.nih.gov/pubmed/26478244

Acta Crystallographica, Section D, Biological Crystallogrophy • April 2013

The structure of brazzein, a sweet-tasting protein from the wild African plant Pentadiplandra brazzeana

Author information

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Abstract

“Brazzein is the smallest sweet-tasting protein and was isolated from the wild African plant Pentadiplandra brazzeana. The brazzein molecule consists of 54 amino-acid residues and four disulfide bonds. Here, the first crystal structure of brazzein is reported at 1.8 Å resolution and is compared with previously reported solution structures. Despite the overall structural similarity, there are several remarkable differences between the crystal and solution structures both in their backbone folds and side-chain conformations. Firstly, there is an additional ß-helix in the crystal structure. Secondly, the atomic r.m.s.d.s between the corresponding C(ß)-atom pairs are as large as 2.0-2.2 Å between the crystal and solution structures. Thirdly, the crystal structure exhibits a molecular shape that is similar but not identical to the solution structures. The crystal structure of brazzein reported here will provide additional information and further insights into the intermolecular interaction of brazzein with the sweet-taste receptor.”

http://www.ncbi.nlm.nih.gov/pubmed/23519673

Food Chemistry • June 2013

Multiple mutations of the critical amino acid residues for the sweetness of the sweet-tasting protein, brazzein

Author information
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Abstract

"We have previously identified critical residues important for sweetness of the sweet protein brazzein by site-directed mutagenesis (Yoon, Kong, Jo, & Kong, 2011). In order to elucidate the interaction mechanisms of brazzein with the sweet taste receptor, we made multiple mutations of three residues (His31 in loop 30-33, Glu36 in ß-strand III, and Glu41 in loop 40-43). We found that all double mutations (H31R/E36D, H31R/E41A and E36D/E41A) made the molecules sweeter than des-pE1M-brazzein and three single mutants. Moreover, the triple mutation (H31R/E36D/E41A) made the molecule significantly sweeter than three double mutants. These results strongly support the hypothesis that brazzein binds to the multisite surface of the sweet taste receptor. Our findings also suggest that mutations reducing the overall negative charge and/or increasing the positive charge favour sweet-tasting protein potency."

http://www.ncbi.nlm.nih.gov/pubmed/23411256

PLoS One • October 2013

Expression of plant sweet protein brazzein in the milk of transgenic mice

Author information

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Abstract

"Sugar, the most popular sweetener, is essential in daily food. However, excessive sugar intake has been associated with several lifestyle-related diseases. Finding healthier and more economical alternatives to sugars and artificial sweeteners has received increasing attention to fulfill the growing demand. Brazzein, which comes from the pulp of the edible fruit of the African plant Pentadiplandra brazzeana Baill, is a protein that is 2,000 times sweeter than sucrose by weight. Here we report the production of transgenic mice that carry the optimized brazzein gene driven by the goat Beta-casein promoter, which specifically directs gene expression in the mammary glands. Using western blot analysis and immunohistochemistry, we confirmed that brazzein could be efficiently expressed in mammalian milk, while retaining its sweetness. This study presents the possibility of producing plant protein-sweetened milk from large animals such as cattle and goats."

http://www.ncbi.nlm.nih.gov/pubmed/24155905

Yi Chuan • June 2009

Fruit-specific expression of sweet protein Brazzein in transgenic tomato plants

Author information

Yin T1, Lu HY, Zhang SL, Liu JM, Chen DM.
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Abstract

“The AGPL1 (ADP-glucose pyrophosphorylase large subunit 1) promoter from watermelon (Citrullus vulgaris S.) has proved to exhibit fruit-specific expression patterns in tomato (Lycopersicon esculentum L.). A plant expression vector harboring sweet-taste protein, Brazzein, directed by AGPL1 promoter, was constructed and transferred into tomato plants through Agrobacterium-mediated transform methods. Histochemical staining assay, PCR screening, Southern blotting analysis and RT-PCR analysis showed that Brazzein gene was successfully integrated into the genome of transgenic tomato plants with stable expression. Sweet-taste fruits were produced under control of fruit-specific AGPL1 promoter, whereas other parameters of fruit quality were largely unchanged.”

http://www.ncbi.nlm.nih.gov/pubmed/19586868

Chemical Senses • October 2009

Design and evaluation of new analogs of the sweet protein brazzein

Author information

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Abstract

“We have previously modeled the interaction of the sweet protein brazzein with the extracellular domains of the sweet taste receptor. Here, we describe the application of that model to the design of 12 new highly potent analogs of brazzein. Eight of the 12 analogs have higher sweetness potency than wild-type brazzein. Results are consistent with our brazzein-receptor interaction model. The model predicts binding of brazzein to the open form of T1R2 in the T1R2-T1R3 heterodimer.”

Full text, graphs, charts and 14 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2745351/

“Brazzein, originally isolated from the fruit of the African plant Pentadiplandra brazzeana Baillon, is the smallest, most heat-stable and pH-stable member of the set of proteins known to have intrinsic sweetness. These properties make brazzein an ideal system for investigating the chemical and structural requirements of a sweet-tasting protein.”

Archives Of Biochemistry And Biophysics • October 1999

Sweetness Determinant Sites of Brazzein, a Small, Heat-Stable, Sweet-Tasting Protein

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Abstract

Brazzein, originally isolated from the fruit of the African plant Pentadiplandra brazzeana Baillon, is the smallest, most heat-stable and pH-stable member of the set of proteins known to have intrinsic sweetness. These properties make brazzein an ideal system for investigating the chemical and structural requirements of a sweet-tasting protein. We have used the three-dimensional structure of the protein (J. E. Caldwell et al. (1998) Nat. Struct. Biol. 5, 427–431) as a guide in designing 15 synthetic genes in expression constructs aimed at delineating the sweetness determinants of brazzein. Protein was produced heterologously in Escherichia coli, isolated, and purified as described in the companion paper (Assadi-Porter, F. M., Aceti, D., Cheng, H., and Markley, J. L., this issue). Analysis by one-dimensional 1H NMR spectroscopy indicated that all but one of these variants had folded properly under the conditions used. A taste panel compared the gustatory properties of solutions of these proteins to those of sucrose and brazzein isolated from fruit. Of the 14 mutations in the des-pGlu1-brazzein background, four exhibited almost no sweetness, six had significantly reduced sweetness, two had taste properties equivalent to des-pGlu1-brazzein (two times as sweet as the major form of brazzein isolated from fruit which contains pGlu1), and two were about twice as sweet as des-pGlu1-brazzein. Overall, the results suggest that two regions of the protein are critical for the sweetness of brazzein: a region that includes the N- and C-termini of the protein, which are located close to one another, and a region that includes the flexible loop around Arg43.

http://www.sciencedirect.com/science/article/pii/S0003986100917260

CHAPTER FORTY-ONE

Carmine • Cochnea Extract

The Peer Review

The cochineal is a scale insect rom which the natural dye carmine is derived. A primarily sessile parasite native to tropical and subtropical South America as well as Mexico and Arizona, this insect lives on cacti, feeding on plant moisture and nutrients. These insects are found on the pads of prickly pear cacti, then are brushed off and dried.

The insect produces carminic acid that deters predation by other insects. Carminic acid, typically 17-24% of dried insects' weight, can be extracted from the body and eggs, then mixed with aluminium or calcium salts to make carmine dye, also known as cochineal.

Today, carmine is primarily used as a colorant in food and in lipstick. The carmine dye was used in Central America in the 15th century for coloring fabrics and became an important export good during the colonial period. After synthetic pigments and dyes such as alizarin were invented in the late 19th century, natural-dye production gradually diminished. Health fears over artificial food additives, however, have renewed the popularity of cochineal dyes, and the increased demand has made cultivation of the insect profitable again, with Peru being the largest exporter. Some towns in the Mexican state of Oaxaca are still working in handmade textiles using this cochineal.

Cochineal dye was used by the Aztec and Maya peoples of Central and North America. Eleven cities conquered by Montezuma in the 15th century paid a yearly tribute of 2000 decorated cotton blankets and 40 bags of cochineal dye each. Production of cochineal is depicted in Codex Osuna. During the colonial period, the production of cochineal grew rapidly. Produced almost exclusively in Oaxaca by indigenous producers, cochineal became Mexico's second-most valued export after silver. Soon after the Spanish conquest of the Aztec Empire, it began to be exported to Spain, and by the 17th century was a commodity traded as far away as India. The dyestuff was consumed throughout Europe and was so highly prized, its price was regularly quoted on the London and Amsterdam Commodity Exchanges. In 1777, French botanist Nicolas-Joseph Thiéry de Menonville, presenting himself as a botanizing physician, smuggled the insects and pads of the Opuntia cactus to Saint Domingue. This particular collection failed to thrive and ultimately died out, leaving the Mexican monopoly intact. After the Mexican War of Independence in 1810–1821, the Mexican monopoly on cochineal came to an end. Large-scale production of cochineal emerged, especially in Guatemala and the Canary Islands; it was also cultivated in Spain and North Africa.

The demand for cochineal fell sharply with the appearance on the market of alizarin crimson and many other artificial dyes discovered in Europe in the middle of the 19th century, causing a significant financial shock in Spain as a major industry almost ceased to exist. The delicate manual labour required for the breeding of the insect could not compete with the modern methods of the new industry, and even less so with the lowering of production costs. The "tuna blood" dye (from the Mexican name for the Opuntia fruit) stopped being used and trade in cochineal almost totally disappeared in the course of the 20th century. The breeding of the cochineal insect has been done mainly for the purposes of maintaining the tradition rather than to satisfy any sort of demand. It has become commercially valuable again. One reason for its popularity is that many commercial synthetic red dyes were found to be carcinogenic.

Traditionally, cochineal was used for colouring fabrics. During the colonial period, with the introduction of sheep to Latin America, the use of cochineal increased, as it provided the most intense colour and it set more firmly on woolen garments than on clothes made of materials of pre-Hispanic origin such as cotton or agave and yucca fibers. In general, cochineal is more successful on protein-based animal fibres (including silk) than plant-based material. Once the European market discovered the qualities of this product, the demand for it increased dramatically. By the beginning of the 17th century, it was traded internationally. Carmine became strong competition for other colourants such as madder root, kermes, Polish cochineal, Armenian cochineal, brazilwood, and Tyrian purple, as they were used for dyeing the clothes of kings, nobles, and the clergy. For the past several centuries, it was the most important insect dye used in the production of hand-woven oriental rugs, almost completely displacing lac. It was also used for painting, handicrafts, and tapestries. Cochineal-coloured wool and cotton are important materials for Mexican folk art and crafts.

Cochineal is used as a fabric and cosmetics dye and as a natural food coloring. It is also used in histology as a preparatory stain for the examination of tissues and carbohydrates. In artists' paints, it has been replaced by synthetic reds and is largely unavailable for purchase due to poor light-fastness. Natural carmine dye used in food and cosmetics can render the product unacceptable to vegetarian or vegan consumers. Many Muslims consider carmine-containing food forbidden (haraam) because the dye is extracted from insects and all insects except the locust are haraam in Islam. Jews also avoid food containing this additive, though it is not treif, and some authorities allow its use because the insect is dried and reduced to powder.

Cochineal is one of the few water-soluble colorants to resist degradation with time. It is one of the most light- and heat-stable and oxidation-resistant of all the natural organic colorants and is even more stable than many synthetic food colors. The water-soluble form is used in alcoholic drinks with calcium carmine; the insoluble form is used in a wide variety of products. Together with ammonium carmine, they can be found in meat, sausages, processed poultry products (meat products cannot be colored in the United States unless they are labeled as such), surimi, marinades, alcoholic drinks, bakery products and toppings, cookies, desserts, icings, pie fillings, jams, preserves, gelatin desserts, juice beverages, varieties of cheddar cheese and other dairy products, sauces, and sweets.

Carmine is considered safe enough for use in eye cosmetics. A significant proportion of the insoluble carmine pigment produced is used in the cosmetics industry for hair- and skin-care products, lipsticks, face powders, rouges, and blushes. A bright red dye and the stain carmine used in microbiology is often made from the carmine extract, too. The pharmaceutical industry uses cochineal to color pills and ointments.

In spite of the widespread use of carmine dyes in food and cosmetic products, a number of people have been found to experience occupational asthma, food and cosmetic allergies (such as allergic rhinitis and cheilitis), IgE-mediated respiratory hypersensitivity, and in rare cases anaphylactic shock. In 2009, the FDA ruled that labels of cosmetics and food that include cochineal extract must include that information on their labels (under the name "cochineal extract" or "carmine"). In 2006, the FDA stated that it found no evidence of a "significant hazard" to the general population. In the EU, authorities list carmine as additive E120 in the list of EU-approved food additives. An artificial cochineal dye is labeled E 124. The directive governing food dyes approves the use of carmine for certain groups of foods only, but it is still found in several products, particularly alcoholic beverages.

Journal Of Investigative Allergology And Clinical Immunology • January 2015

Recurrent Anaphylaxis: A Case of IgE-Mediated Allergy to Carmine Red (E120)

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Full text, link to PDF

http://www.jiaci.org/summary/vol25-issue6-num1279

“Five patients developed clinical symptoms during the placebo-controlled oral challenge. As a result, the overall frequency of clinical carmine allergy is estimated to be 0.7% in general dermatology patients studied for food-associated symptoms. Oral challenge test provides a valuable in vivo tool to better inform patients with positive skin prick tests to additives to avoid false allergy diets.”

European Annals Of Allergy And Clinical Immunology • November 2015

An oral challenge test with carmine red (E120) in skin prick test positive patients

Author information

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Abstract

BACKGROUND
Positive skin prick test reactions to carmine red (E120) occur in approximately 3% of the patients studied for food allergy. Carmine ingestion associated systemic symptoms are occasionally suspected, but sufficient information of proven carmine allergy is not available.

PATIENTS AND METHODS
To analyse carmine related symptoms in skin prick test positive patients a cohort of 23 patients with suspected allergy to carmine red was subjected to a single-blind placebo-controlled oral challenge test with carmine red.

RESULTS
Five patients developed clinical symptoms during the placebo-controlled oral challenge. As a result, the overall frequency of clinical carmine allergy is estimated to be 0.7% in general dermatology patients studied for food-associated symptoms.

CONCLUSIONS
Oral challenge test provides a valuable in vivo tool to better inform patients with positive skin prick tests to additives to avoid false allergy diets.

http://www.ncbi.nlm.nih.gov/pubmed/26549338

Regulatory Toxicology And Pharmacology • December 2015

Health safety issues of synthetic food colorants

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Abstract

“Increasing attention has been recently paid to the toxicity of additives used in food. The European Parliament and the Council published the REGULATION (EC) No. 1333/2008 on food additives establishing that the toxicity of food additives evaluated before 20th January 2009 must be re-evaluated by European Food Safety Authority (EFSA). The aim of this review is to survey current knowledge specifically on the toxicity issues of synthetic food colorants using official reports published by the EFSA and other available studies published since the respective report. Synthetic colorants described are Tartrazine, Quinoline Yellow, Sunset Yellow, Azorubine, Ponceau 4R, Erythrosine, Allura Red, Patent Blue, Indigo Carmine, Brilliant Blue FCF, Green S, Brilliant Black and Brown HT. Moreover, a summary of evidence on possible detrimental effects of colorant mixes on children’s behaviour is provided and future research directions are outlined.”

http://www.ncbi.nlm.nih.gov/pubmed/26404013

European Annals In Allergy And Clinical Immunology • November 2014

New risks from ancient food dyes: cochineal red allergy

Author information

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Abstract

“This study reports an unusual case of IgE-mediated hypersensitivity to Cochineal red or Carmine red, a coloring agent of natural origin. Although the risk of anaphylactic reactions is well known, since the nineties the use of this additive seems to be nowadays on the rise. The problem of labeling of additives used in handmade food products is highlighted.”

http://www.ncbi.nlm.nih.gov/pubmed/25398168

“All dyes significantly reduced cell viability after 3 min of exposure at all concentrations ...”

Ophthalmologica • September 2013

Effect of vital dyes on retinal pigmented epithelial cell viability and apoptosis: implications for chromovitrectomy

Author information
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Abstract

PURPOSE
To investigate the in vitro effect of vital dyes on toxicity and apoptosis in a human retinal pigment epithelial cell line.

METHODS
ARPE-19 cells were exposed to brilliant blue (BBG), Evans Blue (EB), bromophenol blue (BroB), indocyanine green (ICG), infracyanine green (IfCG), light green (LG), fast green (FG), indigo carmine (IC) and Congo red (CR). Balanced salt solution was used as the control. Five different concentrations and 2 exposure times were tested. Cell viability was determined by the MTS (1-solution methyl thiazolyl tetrazolium) assay and apoptosis by Bax expression on Western blot.

RESULTS
All dyes significantly reduced cell viability after 3 min of exposure at all concentrations ($p < 0.01$), except for BBG that was safe at concentrations up to 0.25 mg/ml and CR up to 0.05 mg/ml, while LG was safe at all concentrations. Toxicity was higher after 30 min of exposure. Expression of Bax was upregulated after all dye exposures, except BBG; ICG had the highest Bax expression ($p < 0.01$).

CONCLUSIONS
Overall the safest dye was BBG followed by LG, IfCG, FG, CR, IC, BroB, EB and ICG. ICG was toxic at all concentrations and exposure times tested. Moreover, BBG was the only dye that did not induce apoptosis in ARPE-19 cells.

Full text, graphs, charts and 51 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260821/

B-Ent • January 2012

Carmine red (E-120)-induced occupational respiratory allergy in a screen-printing worker: a case report

Author information

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Immunology - Allergology - Rheumatology
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Abstract

“Here we present a case report of a patient suffering from occupational rhinoconjunctivitis and asthma due to IgE-mediated carmine red allergy. This is the first description of carmine red allergy in a screen-printing worker in which the diagnosis was documented by quantification of specific IgE antibodies, by skin tests, by a flow-assisted basophil activation test, and by a carmine red challenge test.”

http://www.ncbi.nlm.nih.gov/pubmed/23113389

“The results demonstrated that more than 50% of the samples contained aminocarminic acid, evidencing the alarming illicit use of this semi-synthetic carmine acid derivative.”

Food Additive Contamination, Part B, Surveillance • September 2012

Aminocarminic acid in E120-labelled food additives and beverages

Author information

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frodi dei prodotti agroalimentari (ICQRF), Laboratory of Catania, Catania, Italy

Abstract

An analytical method was developed for investigating aminocarminic acid occurrence in E120-labelled red-coloured-beverages and in E120 additives, with the aim of controlling the purity of the carmine additive in countries where the use of aminocarminic acid is forbidden. The carminic acid and the aminocarminic acid were separated by high-performance liquid chromatography-photodiode array-tandem mass spectrography (HPLC-PDA-MS/MS). The method was statistically validated. The regression lines, ranging from 10 to 100 mg/L, showed r(2)> 0.9996. Recoveries from 97% to 101% were obtained for the fortification level of 50 mg/L; the relative standard deviations did not exceed 3%. The LODs were below 2 mg/L, whereas the LOQs did not exceed 4 mg/L. The method was successfully applied to 27 samples of commercial E120-labelled red-coloured beverages and E120 additives, collected in Italy during quality control investigations conducted by the Ministry. The results demonstrated that more than 50% of the samples contained aminocarminic acid, evidencing the alarming illicit use of this semi-synthetic carmine acid derivative.

http://www.ncbi.nlm.nih.gov/pubmed/24786412

“The dyes studied, indigotine, azorubine, and cochineal red, can be potential photoprotectors of manidipine as they quench the excited states of the compound.”

Drug Development And Industrial Pharmacy • March 2010

Indigotine, azorubine, and cochineal red as photoprotectors of manidipine

Author information

Mielcarek J1, Grobelny P, Osmalek T.

Abstract

BACKGROUND

The calcium antagonists from the group of 1,4-dihydropyridine (DHP) derivatives are photolabile, and the products of their photochemical decomposition have no pharmacological activity. Like the other DHP derivatives, after exposure to light, manidipine undergoes decomposition leading to a weakening of the pharmacological activity.

METHOD

The protective influence of selected dyes on manidipine has been tested. The photodegradation of manidipine was performed according to the first version of the ICH Guideline for photostability testing. The solutions were illuminated by a high-pressure lamp HBO-200, and the methods used for evaluation of manidipine photodegradation were HPLC, HPLC-MS, and UV-vis spectrophotometry. Quantitative evaluation of photodegradation was made on the basis of the quantum yields of the processes with the use of Reinecke salt as a chemical actinometer.

RESULTS

Results have shown that all the dyes studied, indigotine, azorubine, and cochineal red, slow down the process of manidipine photodegradation, and the most effective is azorubine. The role of the dyes has been determined on the basis of the Stern-Volmer dependence.

CONCLUSION

The dyes studied, indigotine, azorubine, and cochineal red, can be potential photoprotectors of manidipine as they quench the excited states of the compound.

http://www.ncbi.nlm.nih.gov/pubmed/19663559

“Carmine sensitization without sensitization to mites is seen in one fourth of the patients. Allergic reactions to carmine are not dependent on concurrent reactivity to mites.”

International Archives In Allergy And Immunology • May 2009

Allergy to carmine red (E120) is not dependent on concurrent mite allergy

Author information

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Abstract

BACKGROUND

Positive skin prick test (SPT) reactions to carmine red (E120) have been reported to occur concurrently with reactions to mites. The relationships between positive SPT reactions to carmine, carmine allergy and concurrent mite reactions are unknown. The aim of this study was to analyse the prevalence of carmine sensitization and its clinical importance among patients with suspected allergy to food additives.

METHODS

The occurrence of positive SPT reactions to mites was studied in 6,464 patients: 3,164 were tested with carmine and 2,837 with shrimp. Carmine ingestion-associated symptoms were registered at the time of testing. Patients with positive SPT to carmine received a follow-up questionnaire on their symptoms 1-5 years later.

RESULTS

Positive SPT reactions to carmine were seen in 94 patients (3.0%) of whom 74% also had positive SPT reactions to mites and 22% to shrimp. Carmine ingestion-associated symptoms were not dependent on concurrent mite reactivity in 39/94 (42%) patients.

CONCLUSIONS

Carmine sensitization without sensitization to mites is seen in one fourth of the patients. Allergic reactions to carmine are not dependent on concurrent reactivity to mites.

http://www.ncbi.nlm.nih.gov/pubmed/19439984

“We have, for the first time, identified the major allergen in cochineal extract.
This protein may be a phospholipase or related enzyme,
both of which are known to be allergens in other insects.”

Journal Of Allergy And Clinical Immunology • May 2009

Molecular cloning, expression, and characterization of a major 38-kd cochineal allergen

Author information
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Abstract

BACKGROUND
Carmine is a natural red pigment obtained from dried gravid female cochineal insects (Dactylopius coccus or Coccus cacti). There have been several reports of allergies to carmine, but the major allergens responsible have not been identified.

OBJECTIVE
To identify the major allergenic proteins in cochineal.

METHODS
Immunoblots of purified cochineal extract were probed with sera from 3 patients with allergy. Partial amino acid sequences were determined for the proteins bound by IgE, and the corresponding cDNA, containing a complete coding region, was cloned by 5’ and 3’ rapid cDNA extension and PCR. The recombinant protein was expressed in yeast and subjected to immunoblotting.

RESULTS
We identified a full-length cDNA encoding a protein, which we named CC38K, with 335 amino acids and a molecular mass calculated as 38 kd. This amino acid sequence included all the partial amino acid sequences obtained from the purified proteins identified by IgE from patients with allergy. Recombinant CC38K protein was recognized by patients’ sera, indicating that this is a major allergen present in carmine. The CC38K sequence showed homology to phospholipases.

CONCLUSION
We have, for the first time, identified the major allergen in cochineal extract. This protein may be a phospholipase or related enzyme, both of which are known to be allergens in other insects.

http://www.ncbi.nlm.nih.gov/pubmed/19249084

“This result suggests that superoxide anions, originating on dyes by light irradiation, must attack drug-metabolizing enzymes. It is possible that red cosmetics containing phloxine, erythrosine, or rose bengal react with proteins on skin under lighting and may lead to rough skin.”

Journal Of Environmental Public Health • August 2009

Toxicity of xanthene food dyes by inhibition of human drug-metabolizing enzymes in a noncompetitive manner

By T. Mizutani

Abstract

The synthetic food dyes studied were rose bengal (RB), phroxine (PL), amaranth, erythrosine B (ET), allura red, new coccine, acid red (AR), tartrazine, sunset yellow FCF, brilliant blue FCF, and indigo carmine. First, data confirmed that these dyes were not substrates for CYP2A6, UGT1A6, and UGT2B7. ET inhibited UGT1A6 (glucuronidation of p-nitrophenol) and UGT2B7 (glucuronidation of androsterone). We showed the inhibitory effect of xanthene dye on human UGT1A6 activity. Basic ET, PL, and RB in those food dyes strongly inhibited UGT1A6 activity, with IC(50) values = 0.05, 0.04, and 0.015 mM, respectively. Meanwhile, AR of an acidic xanthene food dye showed no inhibition. Next, we studied the inhibition of CYP3A4 of a major phase I drug-metabolizing enzyme and P-glycoprotein of a major transporter by synthetic food dyes. Human CYP3A4 and P-glycoprotein were also inhibited by basic xanthene food dyes. The IC(50) values of these dyes to inhibit CYP3A4 and P-glycoprotein were the same as the inhibition level of UGT1A6 by three halogenated xanthene food dyes (ET, PL, and RB) described above, except AR, like the results with UGT1A6 and UGT2B7. We also confirmed the noninhibition of CYP3A4 and P-gp by other synthetic food dyes. Part of this inhibition depended upon the reaction of (1)O(2) originating on xanthene dyes by light irradiation, because inhibition was prevented by (1)O(2) quenchers. We studied the influence of superoxide dismutase and catalase on this inhibition by dyes and we found prevention of inhibition by superoxide dismutase but not catalase. This result suggests that superoxide anions, originating on dyes by light irradiation, must attack drug-metabolizing enzymes. It is possible that red cosmetics containing phloxine, erythrosine, or rose bengal react with proteins on skin under lighting and may lead to rough skin.

Full text, graphs, charts and 52 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2778353/

“This manuscript addresses one of the long time problems in the surimi crabstick industry. Various means to control carmine bleeding or color transfer under high temperature for long time pasteurization were demonstrated.”

Journal Of Food Science • November 2009

Controlling the bleeding of carmine colorant in crabstick

Author information

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Abstract

Carmine used to color surimi seafood often seeps or bleeds from red-colored meat to white meat when vacuum-packed products go through high-temperature long-time pasteurization. Various physical and chemical treatments were examined to investigate means to inhibit or minimize carmine bleeding in surimi seafood products. Degree of bleeding was analyzed using L* (lightness) and a* (redness) as affected by carmine concentrations, pH, pasteurization conditions, and added calcium compounds. Bleeding was significantly affected by carmine concentrations. Optimum carmine concentration in color paste was 0.1%. Bleeding increased when pasteurization time and/or temperature increased. Color bleeding was also affected by moisture content of surimi paste. Carmine bleeding was minimized as pH of color solution decreased. The degree of bleeding was controlled as calcium compounds were added in color solution in a descending order of calcium chloride, calcium acetate, and calcium hydroxide. Minimal inhibition was obtained when color solutions contained calcium citrate, tricalcium phosphate, and calcium lactate. Practical Application: This manuscript addresses one of the long time problems in the surimi crabstick industry. Various means to control carmine bleeding or color transfer under high temperature for long time pasteurization were demonstrated. However, further study must continue to stop bleeding completely.

http://www.ncbi.nlm.nih.gov/pubmed/20492104

Biotechnology And Histochemistry • August 2007

The history, chemistry and modes of action of carmine and related dyes

Author information

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Abstract

Carmine has been used in biological staining to demonstrate selectively nuclei, chromosomes or mucins, depending on the formulation. Throughout its history in science, complaints and frustrations have been expressed about dye quality. Inconsistencies in dye quality or identity have prevented thorough understanding of staining mechanisms and have caused many stain solutions to behave unsatisfactorily. The aim of this review is to (1) detail causes of these problems, which are rooted in history, geography and production, (2) offer ways to minimize problems and (3) provide modern explanations for stain behavior. Carmine is a "semi-synthetic" dye, i.e., a complex of aluminum and the natural dye cochineal (carminic acid). Carmine shows considerable batch-to-batch variability. Geography, politics, history, agricultural practices and iconography all contribute to the variability of cochineal. In addition, widely divergent manufacturing methods are used to produce carmine. Also, confusion in terminology has led to mislabeling. Pressure from the food industry for a more satisfactory colorant for acidic foods led to the introduction of a new dye, aminocarminic acid, which could enter the biological market inadvertantly. Improved methods of analysis should help the certification process by the Biological Stain Commission. Further standardization could be achieved by replacing most of the methods of solubilizing carmine. The majority of these methods use heat, which is likely to damage the dye molecule. Fortunately, carmine is readily dissolved by raising the pH of the aqueous solvent above 12, and a new form of the dye, now available commercially, is soluble in water without the need for heat or pH adjustment. Chemical structures and physical properties of carminic acid, carmine, aminocarminic acid and kermesic acid are reviewed. A new configuration for carmine is proposed, as well as possible changes to carminic acid and carmine molecules as a result of decomposition caused by heating. Each of the major classes of carmine-based stains is described as are possible mechanisms of attachment to specific substrates. Glycogen binds carmine through hydrogen bonding, and it is here that carmine decomposed by heat could have the greatest detrimental impact. Nuclei and chromosomes are stained via coordination bonds, perhaps supplemented by hydrogen bonds. Finally, acidic mucins react ionically with carmine. Specificity in the latter case may be due to unique polymeric carmine molecules that form in the presence of aluminum chloride.

http://www.ncbi.nlm.nih.gov/pubmed/18074265

Allergy • December 2007

Case of urticaria due to cochineal dye in red-colored diet

Author information

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Abstract

“We herein describe a 33-year-old female who recurrently exhibited urticaria accompanied by vomiting, diarrhea and dyspnea after taking red-colored food. From her history, we suspected the cochineal dye, the commonly used natural red dye in red-colored food and beverage, to be the cause of her symptoms. Oral provocation test using cochineal dye-stained red-colored boiled-fish-paste induced urticaria and respiratory symptoms. Furthermore the prick tests and the scratch tests with cochineal dye and carminic acid, the major ingredient of cochineal dye, were also positive. These results indicate that type 1 allergy to cochineal dye caused urticaria in this patient. Thereafter, she avoided the foods containing a cochineal dye and showed a complete clinical remission. Recently, the number of literatures described about increased incidence of type 1 allergy to cochineal dye. As the usage of cochineal dye is increasing in the Japanese market, we should keep in mind that cochineal dye can be a cause of urticaria in daily practice.”

http://www.ncbi.nlm.nih.gov/pubmed/18195555

“Carmine is a potential sensitizer in an occupational setting: 18 cases of occupational asthma have been described to date. Carmine allergens are poorly defined; in general, proteins from cochineal not removed by the extraction process are considered as the main allergens in carmine. Our results are consistent with this, but show that these proteins may be subject to chemical modification.”

International Archives Of Allergy And Immunology • November 2005

Occupational asthma to carmine in a butcher

Author information

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Abstract

Hypersensitivity to carmine (E120) has been identified as a cause of food intolerance and occupational asthma. We present a case of occupational asthma following exposure to carmine in a manufacturer of sausages and review the literature.

CASE REPORT

A 42-year-old non-atopic male presented with a 5-year history of rhinoconjunctivitis and asthma on occupational exposure to food additive dusts. Symptoms increased after work. The patient had been exposed for more than 20 years.

METHODS

Skin prick tests were performed with a battery of common inhalant allergens and spices. Cochineal, carmine lake and additive mixes used by the patient were extracted and subsequently used for skin prick test, bronchial provocation and in vitro measurements (specific IgE, Western blot and chromatographic fractionation).

RESULTS

Prick tests were positive to carmine and carmine-containing additives; carmine-specific IgE and bronchial challenge tests were also positive (PC20 = 0.0004 mg/ml and 1.6 kU/l). Western blot showed IgE binding to bands of about 30 kDa on cochineal extract and a diffuse pattern at 40-97 kDa on carmine. This result was confirmed by gel filtration chromatography and dot blot. Carmine completely inhibited IgE binding to cochineal extract.

DISCUSSION

Carmine is a potential sensitizer in an occupational setting: 18 cases of occupational asthma have been described to date. Carmine allergens are poorly defined; in general, proteins from cochineal not removed by the extraction process are considered as the main allergens in carmine. Our results are consistent with this, but show that these proteins may be subject to chemical modification.

http://www.ncbi.nlm.nih.gov/pubmed/16215325

“These data indicate that indigo carmine densitometry is a reliable method for cardiac output determination, but it overestimates circulating blood volume, probably due to the transition of indigo carmine into the extravascular space in the systemic circulation.”

European Journal Of Anaesthesiology • August 2004

Pulse dye densitometry using indigo carmine is useful for cardiac output measurement, but not for circulating blood volume measurement

Author information
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Abstract

BACKGROUND AND OBJECTIVE

We evaluated the validity of a newly developed pulse dye densitometer for indigo carmine for measuring cardiac output and circulating blood volume.

METHODS

Measurements of cardiac output and circulating blood volume were performed with the indigo carmine densitometer during normovolaemia, hypovolaemia and hypervolaemia in nine mongrel dogs under general anaesthesia. The validity was evaluated by comparison of the values of cardiac output and circulating blood volume obtained by the thermodilution technique and the 51Cr-labelled red blood cell method, respectively. We also examined indigo carmine removal by continuous veno-venous haemofiltration after indigo carmine injection.

RESULTS

There was good agreement between dye densitometer- and thermodilution-derived cardiac output ($r = 0.885$, $P < 0.001$). The bias and limits of agreement of these values were 0.09 and+/-1.07 L min(-1) (2 SD, n 22), respectively. The dye-densitometer-derived circulating blood volume was greater than that of the 51Cr-labelled red blood cell method, and both values showed weak agreement ($r = 0.587$, $P < 0.027$). The sieving coefficient of indigo carmine through continuous veno-venous haemofiltration was 0.34+/-0.06.

CONCLUSIONS

These data indicate that indigo carmine densitometry is a reliable method for cardiac output determination, but it overestimates circulating blood volume, probably due to the transition of indigo carmine into the extravascular space in the systemic circulation.

http://www.ncbi.nlm.nih.gov/pubmed/15473618

“The prevalence of sensitization and Occupational Asthma caused by carmine was 41.6% and 8.3%, respectively. When the 3 workers who had left their jobs were included, the cumulative incidence of sensitization and Occupational Asthma was 48.1% and 18.5%, resembling the healthy worker effect.”

Journal Of Allergy And Clinical Immunology • February 2003

Carmine (E-120)-induced occupational asthma revisited

Author information

Tabar-Purroy AI1, Alvarez-Puebla MJ, Acero-Sainz S,
García-Figueroa BE, Echechipía-Madoz S, Olaguibel-Rivera JM, Quirce-Gancedo S.

Abstract

BACKGROUND
Occupational asthma (OA) caused by carmine (E-120) has been reported.

OBJECTIVE
We sought to evaluate the prevalence of sensitization and OA at a natural dye processing factory in which 2 workers had been given a diagnosis of carmine-induced OA 6 years previously.

METHODS
The 24 current employees and one worker who had recently left work because of asthma completed a questionnaire and underwent skin testing (carmine, cochineal, carminic acid, curcuma, annato, and chlorophyll), carmine IgE dot-blot analysis, and methacholine inhalation testing. Workers exhibiting positive occupational skin test responses, work-related asthma, or bronchial hyperresponsiveness underwent specific inhalation challenge and serial peak expiratory flow rate recording.

RESULTS
Positive skin test responses to carmine (41.7%), cochineal (29.2%), and carminic acid (4.2%) were observed. Carmine IgE dot-blot results were positive in 4 subjects. No difference in atopy or smoking was observed between occupationally sensitized and nonsensitized subjects. Among the 5 employees reporting work-related asthma, 2 had positive skin test responses, and 4 had bronchial hyperresponsiveness. Five subjects underwent specific inhalation challenges: 2 workers had early asthma responses to carmine and cochineal challenges, and the remaining subjects did not have suggestive peak expiratory flow recordings. The subject who had left his job was given a diagnosis of carmine-induced OA.

CONCLUSION
The prevalence of sensitization and OA caused by carmine was 41.6% and 8.3%, respectively. When the 3 workers who had left their jobs were included, the cumulative incidence of sensitization and OA was 48.1% and 18.5%, resembling the healthy worker effect. Prevention programs to establish the permissible levels of airborne allergen should be implemented.

http://www.ncbi.nlm.nih.gov/pubmed/12589365

“We find ourselves facing a new example of an allergen that can act through both inhalation and digestion, giving rise to an allergolical syndrome that can show itself clinically with expressions of both respiratory allergy and alimentary allergy.”

Anales del Sistema Sanitario de Navarra • July 2003

Asthma and allergy due to carmine dye

Author information

Tabar AI1, Acero S, Arregui C, Urdánoz M, Quirce S.

Abstract

Cochineal carmine, or simply carmine (E120), is a red colouring that is obtained from the dried bodies of the female insect Dactylopius coccus Costa (the cochineal insect). We have evaluated the prevalence of sensitization and asthma caused by carmine in a factory using natural colouring, following the diagnosis of two workers with occupational asthma. The accumulated incidence of sensitization and occupational asthma due to carmine in this factory are 48.1% and 18.5% respectively, figures that make the introduction of preventive measures obligatory. Occupational asthma caused by inhaling carmine should be considered as a further example of the capacity of certain protein particles of arthropods (in this case cochineal insects) to act as aeroallergens. Carmine should be added to the list of agents capable of producing occupational asthma, whose mechanism, according to our studies, would be immunological mediated by IgE antibodies in the face of diverse allergens of high molecular weight, which can vary from patient to patient. Nonetheless, given the existence of different components in carmine, it cannot be ruled out that substances of low molecular weight, such as carminic acid, might act as haptenes. Besides, since we are dealing with a colouring that is widely used as a food additive, as a pharmaceutical excipient and in the composition of numerous cosmetics, it is not surprising that allergic reactions can appear both through ingestion and through direct cutaneous contact. We find ourselves facing a new example of an allergen that can act through both inhalation and digestion, giving rise to an allergolical syndrome that can show itself clinically with expressions of both respiratory allergy and alimentary allergy.

http://www.ncbi.nlm.nih.gov/pubmed/13679965

“We report on two butchers with occupational asthma due to an IgE-mediated sensitization to carmine. There are several proteins that may act as allergens, and these may be conditioned by the route of exposure and are not cross-reactive with mite proteins. Carmine may be considered to be an etiologic agent in butcher’s asthma.”

International Journal Of Occupational Medicine And Environmental Health • July 2003

Occupational asthma induced by inhaled carmine among butchers

Author information
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Abstract

BACKGROUND
Carmine is a natural coloring agent for food and cosmetics. There have been several reports of occupational asthma among employees at factories making natural dyes, however, there are no cases reported among butchers.

OBJECTIVES
We report on two male patients who presented with a history of occupational asthma. Both patients are butchers and used a mixture of additives with carmine as dye in sausages.

METHODS
Skin prick tests were performed with common aeroallergens, commercial mixture additives and separated compound of the additive mixture. Total IgE, metacholine test, specific inhalatory challenge tests with carmine and mites, SDS-PAGE and IgE-immunoblotting were carried out.

RESULTS
Skin tests were positive to mites, additive mixture and carmine in both cases. Specific IgE to mites was positive only in patient one. Bronchial provocation tests were positive to metacholine and carmine and negative to Dermatophagoides pteronyssinus in both cases. IgE-immunoblot showed a specific IgE-binding band at 10 kDa and at a large number of bands along all molecular weights. No inhibition was achieved in carmine-IgE-specific bands with the D. pteronyssinus extract.

CONCLUSIONS
We report on two butchers with occupational asthma due to an IgE-mediated sensitization to carmine. There are several proteins that may act as allergens, and these may be conditioned by the route of exposure and are not cross-reactive with mite proteins. Carmine may be considered to be an etiologic agent in butcher’s asthma.

http://www.ncbi.nlm.nih.gov/pubmed/12926405

Shokuhin Eiseigaku Zasshi • August 2002

Identification of acid-stable carmine in imported apple syrup product

Author information
Kawasaki Y1, Sugimoto N, Sato K, Yamazaki T, Ishiwata H, Maitani T.
National Institute of Health Sciences: 1-18-1, Kamiyoga, Setagaya-ku, Tokyo 158-850, Japan

Abstract

“An unknown red pigment was purified from an apple syrup product imported from Canada, using a DIAION HP-20 column with methanol as the eluent. By spectroscopic means and chemical synthesis, the isolated pigment was identified as 4-aminocarminic acid, which is the major pigment of acid-stable carmine (a red colorant illegal in Japan). In addition, HPLC and TLC methods were proposed to detect this illegal colorant. While the color of carminic acid changed from yellow to red in the pH range of McIlvaine buffer (3.0-7.0), the color of 4-aminocarminic acid was always red, and also the ultraviolet/visible (UV/Vis) spectra did not change. These characteristics are useful to distinguish 4-aminocarminic acid from carminic acid.”

http://www.ncbi.nlm.nih.gov/pubmed/12436709

Drugs • June 2001

Manidipine: a review of its use in hypertension

Author information

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Abstract

Manidipine is a dihydropyridine calcium antagonist, which causes systemic vasodilation by inhibiting the voltage-dependent calcium inward currents in smooth muscle cells. The resulting reduction in blood pressure (BP) in patients with hypertension is maintained over 24 hours. Manidipine 10 to 40 mg once daily for 4 weeks significantly lowered office BP from baseline and compared with placebo, and significantly reduced 24-hour BP compared with placebo in patients with essential hypertension in a well controlled trial. The decline in BP was maintained over 24 hours (trough to peak BP ratios were >50%) without disturbing the circadian BP pattern. BP reductions with therapeutic dosages of manidipine were maintained for up to 1 year in noncomparative trials. The BP-lowering capacity of manidipine 5 to 20 mg/day appears to be similar to that of other calcium antagonists with which it has been compared in randomised double-blind and nonblind trial. In a well controlled short term trial, manidipine 10 mg daily significantly decreased trough sitting BP compared with placebo in elderly patients with mild to moderate essential hypertension. Decreases in BP were maintained for up to 3 years of treatment. The drug (10 or 20 mglday) also significantly lowered sitting BP from baseline in patients with hypertension and type 2 diabetes mellitus in randomised, long term comparative trials. In general, the observed reduction in BP with manidipine was similar to that observed with amlodipine, enalapril or delapril. The effects of manidipine on urinary albumin excretion (UAE) have not been clearly demonstrated in clinical trials in this patient group. BP was also reduced with manidipine in patients with impaired glucose tolerance. Manidipine was well tolerated in clinical trials, with most adverse effects related to vasodilation. Commonly reported events included ankle oedema, headache. palpitation. flushing, dizziness, rash and fatigue. Manidipine appears to have less potential for pedal oedema than amlodipine.

Manidipine has shown antihypertensive efficacy and appears to be well tolerated in adult and elderly patients with mild or moderate essential hypertension. The BP-lowering effects of the drug in patients with hypertension and type 2 diabetes mellitus or impaired glucose tolerance were not associated with any adverse metabolic effects. The effects of manidipine on UAE in this patient group remain unclear. Manidipine provides an additional treatment option for patients for whom dihydropyridine calcium antagonists are appropriate. Manidipine is a dihydropyridine calcium antagonist, which causes systemic vasodilation by inhibiting the voltage-dependent calcium inward currents in smooth muscle cells. The resulting reduction in blood pressure (BP) in patients with hypertension is maintained over 24 hours. Manidipine 10 to 40mg once daily for 4 weeks significantly lowered office BP from baseline and compared with placebo, and significantly reduced 24-hour BP compared with placebo in patients with essential hypertension in a well controlled trial. The decline in BP was maintained over 24 hours (trough to peak BP ratios were >50%) without disturbing the circadian BP pattern. BP reductions with therapeutic dosages of manidipine were maintained for up to 1 year in non-comparative trials. The BP-lowering capacity of manidipine 5 to 20 mg/day appears to be similar to that of other calcium antagonists with which it has been compared in randomised double-blind and nonblind trial. In a well controlled short term trial, manidipine 10 mg daily significantly decreased trough sitting BP compared with placebo in elderly patients with mild to moderate essential hypertension. Decreases in BP were maintained for up to 3 years of treatment. The drug (10 or 20 mg/day) also significantly lowered sitting BP from baseline in patients with hypertension and type 2 diabetes mellitus in randomised, long term comparative trials. In general, the observed reduction in BP with manidipine was similar to that observed with amlodipine, enalapril or delapril. The effects of manidipine on urinary albumin excretion (UAE) have not been clearly demonstrated in clinical trials in this patient group. BP was also reduced with manidipine in patients with impaired glucose tolerance. Manidipine was well tolerated in clinical trials, with most adverse effects related to vasodilation. Commonly reported events included ankle oedema, headache. palpitation. flushing, dizziness, rash and fatigue. Manidipine appears to have less potential for pedal oedema than amlodipine.

https://www.ncbi.nlm.nih.gov/pubmed/11693466

“We have identified three allergens of around 17, 28, and 50 kilodaltons implicated in occupational asthma of three carmine workers.”

Annals In Allergy, Asthma And Immunology • May 2000

Identification of allergens involved in occupational asthma due to carmine dye

Author information

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Department of Allergy, Hospital Virgen del Camino, Pamplona, Spain

Abstract

BACKGROUND

Carmine has been implicated as an etiologic agent of occupational asthma, but the allergens involved have not been yet identified.

OBJECTIVE

To identify the allergens involved in occupational asthma due to carmine dye.

METHODS

An in vitro study based in SDS-PAGE and IgE immunoblotting with carmine and cochineal extracts was performed. Sera from three carmine dye workers diagnosed with occupational asthma induced by carmine dye and from seven nonatopic subjects were used.

RESULTS

Three proteins of around 30, 28, and 17 kD in raw cochineal extract and another protein of 50 kD in the boiled one were demonstrated by SDS-PAGE. Two proteins of around 50 and 28 kD were observed in the carmine extract by the same technique. Specific IgE binding bands at 17 kD in cochineal raw extract, at 50 kD in the boiled one, and at 28 kD in carmine extract were demonstrated by IgE immunoblotting.

CONCLUSIONS

We have identified three allergens of around 17, 28, and 50 kD implicated in occupational asthma of three carmine workers.

http://www.ncbi.nlm.nih.gov/pubmed/10831011

“... since we are dealing with a colouring that is widely used as a food additive, as a pharmaceutical excipient and in the composition of numerous cosmetics, it is not surprising that allergic reactions can appear both through ingestion and through direct cutaneous contact. We find ourselves facing a new example of an allergen that can act through both inhalation and digestion, giving rise to an allergolical syndrome that can show itself clinically with expressions of both respiratory allergy and alimentary allergy.”

Annals In Allergy, Asthma And Immunology • May 2000

Asthma and allergy due to carmine dye

Author information

Tabar AI1, Acero S, Arregui C, Urdánoz M, Quirce S.
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Abstract

Cochineal carmine, or simply carmine (E120), is a red colouring that is obtained from the dried bodies of the female insect Dactylopius coccus Costa (the cochineal insect). We have evaluated the prevalence of sensitization and asthma caused by carmine in a factory using natural colouring, following the diagnosis of two workers with occupational asthma. The accumulated incidence of sensitization and occupational asthma due to carmine in this factory are 48.1% and 18.5% respectively, figures that make the introduction of preventive measures obligatory. Occupational asthma caused by inhaling carmine should be considered as a further example of the capacity of certain protein particles of arthropods (in this case cochineal insects) to act as aeroallergens. Carmine should be added to the list of agents capable of producing occupational asthma, whose mechanism, according to our studies, would be immunological mediated by IgE antibodies in the face of diverse allergens of high molecular weight, which can vary from patient to patient. Nonetheless, given the existence of different components in carmine, it cannot be ruled out that substances of low molecular weight, such as carminic acid, might act as haptenes. Besides, since we are dealing with a colouring that is widely used as a food additive, as a pharmaceutical excipient and in the composition of numerous cosmetics, it is not surprising that allergic reactions can appear both through ingestion and through direct cutaneous contact. We find ourselves facing a new example of an allergen that can act through both inhalation and digestion, giving rise to an allergolical syndrome that can show itself clinically with expressions of both respiratory allergy and alimentary allergy.

http://www.ncbi.nlm.nih.gov/pubmed/13679965

“Carmine proteins can induce IgE-mediated food allergy and occupational asthma in workers using products where its presence could be easily overlooked, as well as in dye manufacture workers.”

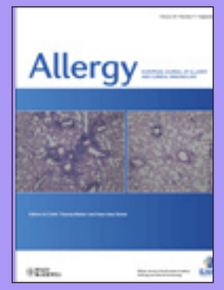
Allergy • September 1998

Occupational asthma and food allergy due to carmine

Author information

Acero S1, Tabar AI, Alvarez MJ, Garcia BE, Olaguibel JM, Moneo I.

Abstract



Carmine (E120), a natural red dye extracted from the dried females of the insect Dactylopius coccus var. Costa (cochineal), has been reported to cause hypersensitivity reactions. We report a case of occupational asthma and food allergy due to carmine in a worker not engaged in dye manufacturing. A 35-year-old nonatopic man, who had worked for 4 years in a spice warehouse, reported asthma and rhinoconjunctivitis for 5 months, related to carmine handling in his work. Two weeks before the visit, he reported one similar episode after the ingestion of a red-colored sweet containing carmine. Peak flow showed drops higher than 25% related to carmine exposure. Prick tests with the cochineal insect and carmine were positive, but negative to common aeroallergens, several mites, foods, and spices. The methacholine test was positive. Specific bronchial challenge test with a cochineal extract was positive with a dual pattern (20% and 24% fall in FEV1). Double-blind oral challenge with E120 was positive. The patient’s sera contained specific IgE for various high-molecular-weight proteins from the cochineal extract, as shown by immunoblotting. Carmine proteins can induce IgE-mediated food allergy and occupational asthma in workers using products where its presence could be easily overlooked, as well as in dye manufacture workers.

Full text, link to PDF

http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.1998.tb03998.x/abstract;jsessionid=14425838CF7CAA5C86195572CFAABB13.f01t04

Allergy • November 1997

Anaphylactic reactions to ingested carmine (E120)

Author information

Wüthrich B1, Kägi MK, Stücker W.

Department of Dermatology, University Hospital, Zurich, Switzerland

Abstract

“We report five cases of anaphylactic reaction to carmine (cochineal, E120) after patients drank an alcoholic beverage. By means of positive skin prick tests (SPT) and positive RAST to carmine. IgE-mediated sensitization could be established. One nonatopic patient showed also a great amount of serum IgE antibodies to the carmine acid-albumin conjugate. Due to its widespread use in the food and cosmetic industry, carmine should be tested in the allergy work-up in case of allergic reactions after a drink or a meal.”

http://www.ncbi.nlm.nih.gov/pubmed/9404569

“The positive skin prick tests to the popsicle and carmine and the successful Prausnitz-Kustner transfer of skin prick test reactivity support a carmine-specific, IgE-mediated mechanism in explaining our patient’s popsicle-induced anaphylaxis.”

Annals In Allergy, Asthma And Immunology • November 1997

Popsicle-induced anaphylaxis due to carmine dye allergy

Author information

Baldwin JL1, Chou AH, Solomon WR.

Department of Internal Medicine, University of Michigan, Ann Arbor, USA

Abstract

BACKGROUND

IgE-mediated hypersensitivity is a suggested mechanism to explain adverse reactions from carmine-containing products.

OBJECTIVE

To describe a patient who experienced anaphylaxis after ingestion of a popsicle colored with carmine and to provide additional evidence that the adverse reaction was IgE-mediated.

METHODS

The patient and her husband underwent skin prick tests to the popsicle and carmine. The patient also received skin prick tests and/or open oral challenge to each of the other components of the incriminated food. Topical application of cosmetics with and without carmine to the patient’s forearm was also performed. To confirm carmine-specific IgE, a Prausnitz-Kustner (P-K) test was performed using the patient’s husband as recipient. Twenty control subjects also were tested to carmine by skin prick test.

RESULTS

The patient showed 4+ skin prick test responses to the popsicle and carmine. Skin prick tests and/or open oral challenge to each of the other components of the popsicle were negative. The patient’s husband’s and 20 control subjects’ skin prick tests to carmine were negative as was the patient’s husband’s skin prick test to the popsicle. Skin prick test reactivity to the popsicle and carmine were successfully transferred to the patient’s husband in P-K format. Cosmetics applied to the patient’s forearm elicited no immediate response.

CONCLUSION

The positive skin prick tests to the popsicle and carmine and the successful (P-K) transfer of skin prick test reactivity support a carmine-specific, IgE-mediated mechanism in explaining our patient’s popsicle-induced anaphylaxis.

http://www.ncbi.nlm.nih.gov/pubmed/9396973

“Recoveries of carminic acid by this assay were > 95% for milk beverage and jelly, and > 85% for yogurt and fish paste. Carminic acid was detected in 7 of 26 red-colored commercial food products and ranged from 3.5 to 356 micrograms/gram.”

J AOAC International • May 1995

Enzyme immunoassay for carminic acid in foods

Author information

Yoshida A1, Takagaki Y, Nishimune T.

Osaka Prefectural Institute of Public Health, Japan

Abstract

A competitive enzyme immunoassay (EIA) for carminic acid was investigated. Monoclonal anticarminic acid antibody was obtained from A/J mice immunized with carminic acid-human immunoglobulin G (IgG) conjugate. Carminic acid was extracted with distilled water from beverage, jelly, candy, pasta sauce, yogurt, or ice cream samples. Ham or fish paste samples were digested with pronase, then carminic acid was extracted from samples with sodium hydroxide solution. The extract was diluted more than 10-fold with 1% gelatin in borate buffer solution. Microtiter plates were coated with carminic acid-bovine serum albumin (BSA) conjugate or just BSA. Goat anti-mouse IgG(H+L)-peroxidase complex was used as a second antibody, and 3,3’,5,5’-tetramethylbenzidine was used as a substrate for the peroxidase. The working range for quantitative analysis was 0.3-10 ng/mL, and the detection limit was 0.2 micrograms/g original sample. Recoveries of carminic acid by this assay were > 95% for milk beverage and jelly, and > 85% for yogurt and fish paste. Carminic acid was detected in 7 of 26 red-colored commercial food products and ranged from 3.5 to 356 micrograms/g. This EIA system also responded to the structural analogue of carminic acid, laccaic acid.

http://www.ncbi.nlm.nih.gov/pubmed/7756895

“These findings suggest that carmine may induce immunologic responses, most likely IgE mediated in workers with symptoms of occupational asthma.”

Journal Of Allergy And Clinical Immunology • January 1994

Occupational asthma and immunologic responses induced by inhaled carmine among employees at a factory making natural dyes

Abstract

Carmine is a natural red dye widely used as a food coloring agent and for cosmetic manufacture. It is extracted from the dried females of the insect Dactylopius coccus var. Costa (cochineal). Although it has been reported that inhalation of carmine may give rise to occupational asthma and extrinsic allergic alveolitis, there is little evidence of its immunogenic capacity. We studied nine current employees at a factory making natural dyes and one former employee who had left this plant after occupational asthma developed. A current employee had work-related symptoms of rhinitis and asthma that were confirmed by bronchial provocation tests, and another worker had rhinitis. Immunologic sensitization to carmine and cochineal was evaluated by means of skin testing and determination of serum-specific IgE and IgG subclass antibodies by RAST and ELISA, respectively. The specificity of the RAST assay was investigated by RAST inhibition with different fractions of carmine. The three workers with respiratory symptoms had positive skin prick test reactions to both carmine and cochineal. An immediate response to the bronchial provocation test with carmine and cochineal was observed in the current employee with asthma. Specific IgE antibodies against carmine and cochineal were found only in this worker. RAST inhibition studies indicated that the main allergen had a molecular weight between 10 and 30 kd. Specific IgG antibodies against carmine and cochineal, mainly the subclasses IgG1, IgG3, and IgG4, were found in the 10 subjects surveyed. These findings suggest that carmine may induce immunologic responses, most likely IgE mediated in workers with symptoms of occupational asthma.

http://www.ncbi.nlm.nih.gov/pubmed/8308181

Food Chemistry And Toxicology • September 1992

Genotoxicity studies in vitro and in vivo on carminic acid (natural red 4)

Author information

Loprieno G1, Boncristiani G, Loprieno N.

Dipartimento di Scienze dell'Ambiente e del Territorio, The University, Pisa, Italy

Abstract

"The potential genotoxic activity of carminic acid (CAS no. 1260-17-9; EINECS no. 215-023-3; C.I. no. 75410), a component of natural red colouring products (cochineal: CAS no. 1343-78-8; EINECS no. 215-680-6; C.I. no. 75470), used in food, cosmetics and drugs, has been evaluated by means of a series of short-term tests in vitro and in vivo, namely Salmonella reverse mutation, chromosome aberrations and sister chromatid exchanges in vitro on Chinese hamster ovary cells, and the mouse micronucleus test. All studies have produced negative results. The data obtained strongly support the non-mutagenic/non-carcinogenic activity of this compound. Genotoxicity data previously obtained for carminic acid, concerning the induction of a series of other genetic endpoints in different test systems, have also been considered, as have recent findings that indicate lack of carcinogenic activity in the cochineal preparation containing 29.8% carminic acid."

http://www.ncbi.nlm.nih.gov/pubmed/1385283

Food Chemistry And Toxicology • September 1991

Carcinogenicity study of cochineal in B6C3F1 mice

Author information
Mori H1, Iwata H, Tanaka T, Morishita Y, Mori Y, Kojima T, Okumura A.
Department of Pathology, Gifu University School of Medicine, Japan

Abstract

“The carcinogenicity of cochineal, a red colouring used in food and other products, was studied in a 2-yr bioassay in B6C3F1 mice. Groups of 50-55 mice of each sex were given 0, 3 or 6% cochineal in the diet for 2 yr. Mice of all groups developed tumours including hepatocellular adenomas or carcinomas, pulmonary adenomas or adenocarcinomas and lymphomas or lymphatic leukaemias, and the incidences of these tumours were not significantly different in treated and control groups. The results indicate that cochineal lacks carcinogenicity in mice and are consistent with those of in vitro short-term assays of cochineal and of carminic acid, an active principle of cochineal.”

http://www.ncbi.nlm.nih.gov/pubmed/1937288

Journal Of The Association Of Official Analytical Chemists • March 1989

Liquid chromatographic determination of carminic acid in yogurt

Author information

Jalón M1, Peña MJ, Rivas JC.

Universidad de Salamanca, Departamento de Química Analítica, Nutrición y Bromatología, España

Abstract

“A reverse-phase liquid chromatographic method is described for the determination of carminic acid in yogurt. A C18 column is used with acetonitrile-1.19M formic acid (19 + 81) as mobile phase and diode array detection. Sample preparation includes deproteinization with papain and purification in a polyamide column. The relative standard deviation for repeated determinations of carminic acid in a commercial strawberry-flavored yogurt was 3.0%. Recoveries of carminic acid added to a natural-flavored yogurt ranged from 87.2 to 95.3% with a mean of 90.2%. The method permits measurement of amounts as low as 0.10 mg/kg.”

http://www.ncbi.nlm.nih.gov/pubmed/2708269

Biochemistry And Biophysical Research Communications • March 1983

Red dye No. 2 and the red pigment carmine enhance aryl hydrocarbon hydroxylase and guanylate cyclase activities

Rochat MH, Vesely DL.

Abstract

"The food coloring amaranth (F, D and C red No. 2) and the red pigment carmine, but not erythrosine (F, D and C red No. 3), caused a twofold enhancement of two enzymes (aryl hydrocarbon hydroxylase and guanylate cyclase) that have been linked with chemical carcinogenesis. Dose response relationships revealed that carmine enhanced both enzymes to near maximal levels at concentrations as low as 1 to 10 nM while amaranth needed a concentration of 100 nM to cause a maximal enhancement. These data suggest that amaranth and carmine mimic the effects of some chemical carcinogens at the cellular level, but erythrosine does not mimic any of these effects."

http://www.ncbi.nlm.nih.gov/pubmed/6132603

CHAPTER FORTY-TWO

Lactose

The Peer Review

Ruminant milk and dairy products are important food resources in many European, African, and Middle Eastern societies. These regions are also associated with derived genetic variants for lactase persistence. In mammals, lactase, the enzyme that hydrolyzes the milk sugar lactose, is normally down-regulated after weaning, but at least five human populations around the world have independently evolved mutations regulating the expression of the lactase-phlorizin-hydrolase gene. These mutations result in a dominant lactase persistence phenotype and continued lactase tolerance in adulthood. A single nucleotide polymorphism (SNP) at C/T-13910 is responsible for most lactase persistence in European populations, but when and where the T-13910 polymorphism originated and the evolutionary processes by which it rose to high frequency in Europe have been the subject of strong debate. A history of dairying is presumed to be a prerequisite, but archaeological evidence is lacking. In this study, DNA was extracted from the dentine of 36 individuals excavated at a medieval cemetery in Dalheim, Germany. Eighteen individuals were successfully genotyped for the C/T-13910 SNP by molecular cloning and sequencing, of which 13 (72%) exhibited a European lactase persistence genotype: 44% CT, 28% TT. Previous ancient DNA-based studies found that lactase persistence genotypes fall below detection levels in most regions of Neolithic Europe. Our research shows that by AD 1200, lactase persistence frequency had risen to over 70% in this community in western Central Europe. Given that lactase persistence genotype frequency in present-day Germany and Austria is estimated at 71-80%, our results suggest that genetic lactase persistence likely reached modern levels before the historic population declines associated with the Black Death, thus excluding plague-associated evolutionary forces in the rise of lactase persistence in this region. This new evidence sheds light on the dynamic evolutionary history of the European lactase persistence trait and its global cultural implications.

Full text, graphs, charts and 50 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3900515/

Pakistan Journal Of Pharmaceutical Science • January 2016

The incidence of infants with rotavirus enteritis combined with lactose intolerance

Author information
Hu Y1, Gui L1, Chang J1, Liu J1, Xu S1,
Deng C1, Yu F1, Ma Z1, Wang G1, Zhang C1.
Neonatal Department, Maternal and Child Health Hospital of Zhengzhou City, Zhengzhou City, Henan Province, China

Abstract

“This study was to research the incidence of infants with rotavirus enteritis combined with lactose intolerance and the clinical effect of low lactose milk powder for infantile rotavirus enteritis with lactose intolerance. The control groups were 126 cases of infants with diarrhea randomly collected from our hospital at the same period, which their rotavirus detection was negative. The observation group was 185 cases of infants with rotavirus, which was tested to be positive. Through the urine galactose determination, 62 cases of the control group were positive and 124 cases of the observation group were positive. Then 124 cases of infants with rotavirus combined with lactose intolerance were randomly divided into two groups. 60 cases in the control group were given rehydration, correction of acidosis, oral smecta, Intestinal probiotics and other conventional treatment, then continued to the original feeding method. While, 64 cases in the treatment group, on the basis of routine treatment, applied the low lactose milk feeding. To observe the total effective rate for the two groups. The incidence of lactose intolerance in children with rotavirus enteritis (67.03%) was significantly higher than that of children with diarrhea (49.2%), which was tested to be negative. And the difference was statistically significant ($p<0.5$). In the aspect of reducing the frequency of diarrhea, and diarrhea stool forming time, the treatment group has the obvious superiority. The total effective rate was 95.4% for treatment group, which was higher than that in the control group (76.7%), the difference was statistically significant ($P<0.05$).

CONCLUSION

Infants with rotavirus enteritis was easier to merge with lactose intolerance. The low lactose milk powder could improve the therapeutic effectively and could reduce the duration of disease, and restored to normal diet for 2 weeks feeding time.”

http://www.ncbi.nlm.nih.gov/pubmed/27005498

“The study confirms that Lactose Intolerance should not be regarded as an isolated illness but considered a possible trigger for further diseases.”

Annals In Gastroenterology • April 2016

Do patients with lactose intolerance exhibit more frequent comorbidities than patients without lactose intolerance? An analysis of routine data from German medical practices

Author information
Schiffner R1, Kostev K2, Gothe H3.

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2. IMS Health, Epidemiology, Frankfurt am Main, Germany (Karel Kostev) Hall in Tirol, Austria
3. Institute of Public Health, Medical Decision Making and Health Technology Assessment, UMIT, University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria
Chair of Health Sciences/Public Health, Faculty of Medicine “Carl Gustav Carus”, University of Technology Dresden, Dresden, Germany (Holger Gothe) Hall in Tirol, Austria

Abstract

BACKGROUND

The increase in food intolerances poses a burgeoning problem in our society. Food intolerances not only lead to physical impairment of the individual patient but also result in a high socio-economic burden due to factors such as the treatment required as well as absenteeism. The present study aimed to explore whether lactose intolerant (LI) patients exhibit more frequent comorbidities than non-LI patients.

METHODS

The study was conducted on a case-control basis and the results were determined using routine data analysis. Routine data from the IMS Disease Analyzer database were used for this purpose. A total of 6,758 data records were processed and analyzed.

RESULTS

There were significant correlations between LI and the incidence of osteoporosis, changes in mental status, and the presence of additional food intolerances. Comparing 3,379 LI vs. 3,379 non-LI patients, 34.5% vs. 17.7% ($P<0.0001$) suffered from abdominal pain; 30.6% vs. 17.2% ($P<0.0001$) from gastrointestinal infections; and 20.9% vs. 16.0% ($P=0.0053$) from depression. Adjusted odds ratios (OR) were the highest for fructose intolerance (n=229 LI vs. n=7 non-LI; OR 31.06; $P<0.0001$), irritable bowel syndrome (n=247 LI vs. n=44 non-LI; OR 5.23; $P<0.0001$), and bloating (n=351 LI vs. n=68 non-LI; OR 4.94; $P<0.0001$).

CONCLUSION

The study confirms that LI should not be regarded as an isolated illness but considered a possible trigger for further diseases. Additional research is necessary to assert more precise statements.

Full text, graphs, charts and 29 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4805737/pdf/AnnGastroenterol-29-174.pdf

“The incidence of lactase deficiency is high in neonates, and diarrhea due to lactose intolerance tends to occur.”

Zhongguo Dang Dai Er Ke Za Zhi • April 2016

Lactose intolerance in neonates with non-infectious diarrhea

Author information

Su HM1, Jiang Y, Hu YL, Yang H, Dong TJ.

Department of Pediatrics, Peking University First Hospital, Beijing 100034, China

Abstract

OBJECTIVE

To investigate the development of lactose intolerance in neonates with non-infectious diarrhea and its association with diarrhea, and to evaluate the diagnostic values of fecal pH value and urine galactose determination for neonatal lactase deficiency.

METHODS

Seventy hospitalized neonates who developed non-infectious diarrhea between October 2012 and June 2015 were enrolled as the diarrhea group, and 162 hospitalized neonates without non-infectious diarrhea were enrolled as the non-diarrhea group. Test paper was used to determine fecal pH value. The galactose oxidase method was used to detect urine galactose. The neonates with positive galactose oxidase were diagnosed with lactase deficiency, and those with lactase deficiency and diarrhea were diagnosed with lactose intolerance. According to the results of urine galactose detection, 69 neonates in the diarrhea group who underwent urine galactose detection were classified into lactose intolerance group (45 neonates) and lactose tolerance group (24 neonates), and their conditions after treatment were compared between the two groups. The follow-up visits were performed for neonates with diarrhea at 3 months after discharge.

RESULTS

Fecal pH value and positive rate of urine galactose (65% vs 54%) showed no significant differences between the diarrhea and non-diarrhea groups ($P>0.05$). Fecal pH value showed no significant difference between the lactose intolerance and lactose tolerance groups ($P>0.05$), while the neonates in the lactose intolerance group had a significantly longer time to recovery of defecation than those in the lactose tolerance group ($P<0.05$).

CONCLUSIONS

The incidence of lactase deficiency is high in neonates, and diarrhea due to lactose intolerance tends to occur. Determination of fecal pH value has no significance in the diagnosis of lactose intolerance in neonates with diarrhea.

http://www.ncbi.nlm.nih.gov/pubmed/27097573

“The present study has found that this unique DDS-1 strain of Lactobacillus acidophilus, manufactured by Nebraska Cultures, is safe to consume and improves abdominal symptom scores compared to placebo with respect to diarrhea, cramping, and vomiting during an acute lactose challenge.”

Nutrition Journal • May 2016

The effects of the DDS-1 strain of lactobacillus on symptomatic relief for lactose intolerance— a randomized, double-blind, placebo-controlled, crossover clinical trial

Pakdaman MN1, Udani JK2, Molina JP3, Shahani M4.

Abstract

BACKGROUND

Lactose intolerance is a form of lactose maldigestion where individuals experience symptoms such as diarrhea, abdominal cramping, flatulence, vomiting and bowel sounds following lactose consumption. Lactobacillus acidophilus is a species of bacteria known for its sugar fermenting properties. Preclinical studies have found that Lactobacillus acidophilus supplementation may assist in breaking down lactose; however, no human clinical trials exist evaluating its efficacy in alleviating symptoms related to lactose intolerance.

OBJECTIVE

The aim of this randomized, double-blind, placebo-controlled, crossover study was to evaluate the effect of a proprietary strain of Lactobacillus acidophilus on relieving discomfort related to lactose intolerance.

METHODS

The study enrolled healthy volunteers between 18 and 75 years of age who complained of lactose intolerance. Screening visits included a lactose challenge visit to confirm eligibility based on a score of 10 or higher on subjective assessment of the following symptoms after lactose challenge: diarrhea, abdominal cramping, vomiting, audible bowel sounds, flatulence, and overall symptoms. Qualified subjects participated in a 2-arm crossover design, with each arm consisting of 4 weeks of intervention of either active or placebo product, with a 2-week washout period during crossover. The study product consisted of the DDS-1 strain of Lactobacillus acidophilus (Nebraska Cultures, Walnut Creek, California). The placebo was formulated from maltodextrin. Study participants were instructed to take the product once daily for 4 weeks. Data collected included subjective symptom scores related to lactose intolerance.

RESULTS

Longitudinal comparison between the DDS-1 group and placebo group demonstrated statistically significant reductions in abdominal symptom scores during the 6-h Lactose Challenge at week 4 for diarrhea ($p=0.033$), abdominal cramping ($p=0.012$), vomiting ($p=0.0002$), and overall symptom score ($p=0.037$). No adverse events were reported.

CONCLUSIONS

The present study has found that this unique DDS-1 strain of Lactobacillus acidophilus, manufactured by Nebraska Cultures, is safe to consume and improves abdominal symptom scores compared to placebo with respect to diarrhea, cramping, and vomiting during an acute lactose challenge.

Full text with 54 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4875742/pdf/12937_2016_Article_172.pdf

“... both self-perception of lactose intolerance and objective lactose malabsorption are associated with poorer perceived quality of life.”

European Journal Of Clinical Nutrition • May 2016

Perception of lactose intolerance impairs health-related quality of life

Author information

Casellas F1, Aparici A1, Pérez MJ1, Rodríguez P1.

Digestive System Research Unit, Hospital Universitari Vall d’Hebron, Barcelona, Spain

Abstract

BACKGROUND/OBJECTIVES

Chronic conditions impair perception of well-being. Malabsorption of lactose is the most frequent form of malabsorption and manifests as lactose intolerance. There is a lack of information regarding their impact on self-perception of health. The objective of this study is to determine the subjective impact of self-reported lactose intolerance or objective lactose malabsorption on patient health by using a patient-reported outcome to measure health-related quality of life (HRQOL) and modification of lactose-containing food diet.

SUBJECTS/METHODS

A 3-year prospective, cross-sectional study was performed in patients referred for a lactose hydrogen breath test. Patients were asked about their subjective opinion relative to their lactose tolerance and completed a validated, specific questionnaire to determine symptoms of intolerance during habitual consumption of dairy. A 50-g lactose breath test was then performed. Patients were grouped as absorbers vs malabsorbers and tolerant vs intolerants.

RESULTS

A total of 580 patients were included (median age 30 years, 419 female). Overall, 324 patients (56%) considered themselves lactose intolerant and that perception was associated with avoidance of dairy consumption (55% vs only 9% of self-defined tolerants). Self-perception of intolerance was associated with lower HRQOL scores (median, 60 vs 70, $P<0.01$). In contrast, lactose objective malabsorption was not clearly associated with dairy avoidance (41% of malabsorbers avoided dairy vs 31% of absorbers). However, HRQOL scores were also significantly lower in malabsorbers than in absorbers (60 vs 70 respectively, $P<0.001$).

CONCLUSIONS

Subjective perception of lactose intolerance affects the decision to avoid dairy even more than objective malabsorption. However, both self-perception of lactose intolerance and objective lactose malabsorption are associated with poorer perceived quality of life.

http://www.ncbi.nlm.nih.gov/pubmed/27188918

Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz • June 2016

Food intolerances caused by enzyme defects and carbohydrate malassimiliations: Lactose Intolerance & Co.

Author information

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Abstract

“Apart from allergic conditions, carbohydrate malassimiliations (sugar metabolism disorders) are classified within the group of food intolerances. These dose-dependent, yet non-immunological reactions require gastro-enterological or internal diagnosis following nutritional therapy. Intolerances to carbohydrates such as lactose (milk sugar) and fructose (fruit sugar) in addition to sugar alcohols (sorbitol, mannitol, lactitol etc.) have been gaining increasing attention in recent decades as they are the cause of a wide range of gastrointestinal symptoms. There are currently various options for both diagnosis and therapy that differ notably in terms of effort, costs, and efficiency. Nutritional change and patient education are the bases of therapy. Non-observance of the trigger will result in increasing complaints and possibly even more infections, e.g., diverticula, rectal disorders, bacterial miscolonization, bile acid malabsorption). For an optimal therapy, the following sugar metabolism disorders have to be differentiated: hypolactasia versus lactose maldigestion, fructose malabsorption versus fructose overload, combined lactose and fructose intolerance, and isolated adverse reactions against sorbitol.For the medical conditions listed above, a three- or four-stage treatment regimen is recommended. Extensive dietary restrictions with regard to the relevant sugar, except for lactose, should not be maintained over a longer period of time.”

http://www.ncbi.nlm.nih.gov/pubmed/27188621

Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz • June 2016

Food Allergy and Intolerance: Distinction, Definitions and Delimitation

Author information

Kleine-Tebbe J1, Waßmann-Otto A2, Mönnikes H3.

1. Allergie- und Asthma-Zentrum Westend, Praxis Hanf, Ackermann u. Kleine-Tebbe, Spandauer Damm 130, Haus 9, 14050, Berlin, Deutschland
2. Ernährungsberatung und-therapie, Dermatologisches Ambulatorium Hamburg-Alstertal, Hamburg, Deutschland
3. Martin-Luther-Krankenhaus, Klinik für Innere Medizin, Berlin, Deutschland

Abstract

“Immunologically mediated hypersensitivity to foods is defined as food allergy, mainly due to immunglobulins of class E (IgE) triggering immediate reactions (type I hypersensitivity) with possible involvement of mucosa, skin, airways, intestinal tract, and the vascular system. Primary food allergy is based on (early) IgE sensitization against animal (e. g., cow’s milk, hen’s eggs) or plant proteins (e. g. peanut, hazelnut or wheat). In the case of secondary food allergies, IgE against pollen proteins (e. g., birch) reacts to structurally related food proteins (with cross-reactions to stone and pit fruits). Non-immunological food intolerance reactions are mostly based on carbohydrate malassimilation (e. g., lactose intolerance, fructose malabsorption) and are rarely due to pseudo-allergies (e. g., flavors, dyes, preservatives) primarily in patients with chronic urticaria. Common intestinal symptoms are mainly due to functional disorders (e. g., irritable bowel disease), rarely because of inflammatory intestinal diseases (e. g., celiac disease). Histamine intolerance, gluten hypersensitivity, and so-called food type III hypersensitivities are controversial diagnoses. The aforementioned disease entities/models are of variable importance for the affected individuals, the public health system, and society in general.”

http://www.ncbi.nlm.nih.gov/pubmed/27215624

“The French paradox - high saturated fat consumption but low incidence of cardiovascular disease ...”

Medical Hypotheses • July 2016

Dairy products and the French paradox: Could alkaline phosphatases play a role?

By J.P. Lallès

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Abstract

The French paradox - high saturated fat consumption but low incidence of cardiovascular disease (CVD) and mortality - is still unresolved and continues to be a matter of debate and controversy. Recently, it was hypothesised that the high consumption of dairy products, and especially cheese by the French population might contribute to the explanation of the French paradox, in addition to the “(red) wine” hypothesis. Most notably this would involve milk bioactive peptides and biomolecules from cheese moulds. Here, we support the “dairy products” hypothesis further by proposing the “alkaline phosphatase” hypothesis. First, intestinal alkaline phosphatase (IAP), a potent endogenous anti-inflammatory enzyme, is directly stimulated by various components of milk (e.g. casein, calcium, lactose and even fat). This enzyme dephosphorylates and thus detoxifies pro-inflammatory microbial components like lipopolysaccharide, making them unable to trigger inflammatory responses and generate chronic low-grade inflammation leading to insulin resistance, glucose intolerance, type-2 diabetes, metabolic syndrome and obesity, known risk factors for CVD. Various vitamins present in high amounts in dairy products (e.g. vitamins A and D; methyl-donors: folate and vitamin B12), and also fermentation products such as butyrate and propionate found e.g. in cheese, all stimulate intestinal alkaline phosphatase. Second, moulded cheeses like Roquefort contain fungi producing an alkaline phosphatase. Third, milk itself contains a tissue nonspecific isoform of alkaline phosphatase that may function as IAP. Milk alkaline phosphatase is present in raw milk and dairy products increasingly consumed in France. It is deactivated by pasteurization but it can partially reactivate after thermal treatment. Experimental consolidation of the “alkaline phosphatase” hypothesis will require further work including: systematic alkaline phosphatase activity measurements in dairy products, live dairy ferments and intestine of model animals. Furthermore, stool residual IAP, a possible early marker of diabetes, should be assayed in human cohorts. If confirmed, this “alkaline phosphatase” hypothesis will highlight the protective effects of milk alkaline phosphatase and promote the consumption of (microbiologically safe) raw milk and dairy products. Microorganisms secreting alkaline phosphatases may be privileged as ferments in dairy products.

http://www.ncbi.nlm.nih.gov/pubmed/27241245

Asia Pacific Journal Of Clinical Nutrition • January 2015

Lactose nutrition in lactase nonpersisters

Author information

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Abstract

“Lactose handling by the human gut by most people, beyond being breast-fed, has been considered a disorder rather than physiological. A non-human mammalian milk source is novel for the majority. During the first 6 months of life, when neonates and infants are best breast-fed, lactose along with other macronutrients, provides energy, but may have other functions as well. At birth, babies are endowed with their mother’s vaginal microbiome, but not if they are born by Caesarean section. How much maternal milk lactose survives the infant’s small intestine and is processed by this unique gut microbiome and to what end is still uncertain, but no lactose or galactose appears in the faeces. Once intestinal lactase activity declines in most infants, lactose may enhance innate immunity through the cathelicidin antimicrobial peptide (CAMP), which is best achieved by lactose synergy with other colonic fermentation metabolites such as butyrate. It is of interest whether this lactose function or a variant of it persists. It might not be evident when lactase is persistent, as it is in most people of northern European ancestry. Population genomics indicate that lactase persistence became prevalent only about 3000-1000 BC, the Bronze Age of Eurasia. Gastrointestinal symptoms (GIS) in lactase nonpersisters who consume dairy foods are partly dose dependent and not usually evident with single lactose intakes≤25 g per day. Spreading intake across the day reduces the risk as can various dietary patterns. Nevertheless, individual differences in GIS lactose sensitivity may merit public health and clinical consideration.”

http://www.ncbi.nlm.nih.gov/pubmed/26715080

“Up to 25 grams of lactose at any one time can usually be consumed by a lactase non-persistent person, but its food and meal pattern context, the microbiomic characteristics, age and other factors may alter tolerance. Thus, the notion that lactose intolerance is a disorder or disease of lactase non-persistent people is misplaced and has been one of cultural perspective. What actually matters is whether a particular dairy product as normally consumed give rise to symptoms. It is, therefore, proposed that lactose tolerance tests be replaced with dairy food tolerance tests.”

Asia Pacific Journal Of Clinical Nutrition • July 2015

From ‘lactose intolerance’ to ‘lactose nutrition’

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Abstract

The concept of lactose intolerance has become embedded in Western medicine and developing economy medicine. It is based on evidence that intestinal lactase activity persists into later childhood and throughout life in only a minority of the world’s population, notably northern European-derived populations. These people have the T single nucleotide polymorphism (SNP) of the rs49882359 allele (C/T), also known as C/T-13910, the MCM6 gene which positively influences the lactase LCT gene. Other lactase persistent (LP) populations are found in Africa and the Middle East with different genetic variants. These SNPs represent co-evolution with dairying since the agricultural revolution and nutrient-dependent ecological adaptation. That said, gastrointestinal symptoms considered due to small intestinal lactose malabsorption are poorly correlated with lactase non-persistence (LNP), the situation for most people. With LNP, colonic microbiome lactase enables lactose fermentation to occur so that none is found in faeces. Whether the short chain fatty acids (SCFAs) and gases (hydrogen, carbon dioxide and methane) produced cause symptoms is dose-dependent. Up to 25 g of lactose at any one time can usually be consumed by a LNP person, but its food and meal pattern context, the microbiomic characteristics, age and other factors may alter tolerance. Thus, the notion that lactose intolerance is a disorder or disease of LNP people is misplaced and has been one of cultural perspective. What actually matters is whether a particular dairy product as normally consumed give rise to symptoms. It is, therefore, proposed that lactose tolerance tests be replaced with dairy food tolerance tests.

Full text with 57 references

http://apjcn.nhri.org.tw/server/APJCN/24%20Suppl%201//S1.pdf

Advances In Clinical And Experimental Medicine • September 2015

Prevalence of Lactose Malabsorption and Lactose Intolerance in Pediatric Patients with Selected Gastrointestinal Diseases

Author information

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Abstract

BACKGROUND

Lactase is an enzyme involved in the hydrolysis of lactose. Deficiency of the enzyme (hypolactasia) may be determined genetically or arise secondarily to disease of small intestine. Under this condition, lactose enters the colon where it is fermented by intestinal microflora and turns to gases and short-chain fatty acids, causing gastrointestinal symptoms known as lactose intolerance (LI).

OBJECTIVES

To investigate the incidence of lactose malabsorption (LM), LI and the coexistence of these two conditions in children with upper gastrointestinal tract diseases (UGTD), malabsorption syndrome, inflammatory bowel disease (IBD) and functional gastrointestinal disorders (FGID).

MATERIAL AND METHODS

Hydrogen breath test (HBT) was conducted in 387 pediatric patients in years 2010-2013. Two hundred thirty two children with gastrointestinal tract diseases were selected and assigned to groups - UGTD, malabsorption syndrome, IBD or FGID. For each group the frequency of LM, frequency and severity of LI and the frequency of their co-occurrence were calculated.

RESULTS

Lactose malabsorption was observed in 37.08% of patients with gastrointestinal diseases. Positive HBT result was the most common in children with malabsorption syndrome (52.50%) and less common in UGTD (30.85%), especially in ulcer disease (23.53%). Symptoms after lactose ingestion affected 36.64% of the subjects, and were more specific to lactose malabsorbers than to lactose absorbers (72.10% vs. 15.75%). The higher frequency of LI was noted in children with FGID, especially in irritable bowel syndrome (IBS) (65.22%). The lowest incidence of symptoms was obtained in children with UGTD, especially in those with ulcer disease (27.44%). The incidence of LM with LI was noted in 27.16% of all patients and was the highest in IBS (47.83%) and the lowest in ulcer disease (15.78%).

CONCLUSIONS

Lactose malabsorption is a common problem in children with gastrointestinal diseases, especially in children with bowel diseases. Lactose intolerance is related to LM, but does not affect all malabsorbers.

Full text, graphs, charts and 30 references

http://www.advances.am.wroc.pl/pdf/2015/24/5/863.pdf

“Lactase is an enzyme involved in the hydrolysis of lactose. Deficiency of the enzyme (hypolactasia) may be determined genetically or arise secondarily to disease of small intestine. Under this condition, lactose enters the colon where it is fermented by intestinal microflora and turns to gases and short-chain fatty acids, causing gastrointestinal symptoms known as lactose intolerance (LI). Lactose malabsorption is a common problem in children with gastrointestinal diseases, especially in children with bowel diseases.”

PLoS One • January 2014

Ancient DNA analysis reveals high frequency of European lactase persistence allele (T-13910) in medieval Central Europe

Author information

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Abstract

Ruminant milk and dairy products are important food resources in many European, African, and Middle Eastern societies. These regions are also associated with derived genetic variants for lactase persistence. In mammals, lactase, the enzyme that hydrolyzes the milk sugar lactose, is normally down-regulated after weaning, but at least five human populations around the world have independently evolved mutations regulating the expression of the lactase-phlorizin-hydrolase gene. These mutations result in a dominant lactase persistence phenotype and continued lactase tolerance in adulthood. A single nucleotide polymorphism (SNP) at C/T-13910 is responsible for most lactase persistence in European populations, but when and where the T-13910 polymorphism originated and the evolutionary processes by which it rose to high frequency in Europe have been the subject of strong debate. A history of dairying is presumed to be a prerequisite, but archaeological evidence is lacking. In this study, DNA was extracted from the dentine of 36 individuals excavated at a medieval cemetery in Dalheim, Germany. Eighteen individuals were successfully genotyped for the C/T-13910 SNP by molecular cloning and sequencing, of which 13 (72%) exhibited a European lactase persistence genotype: 44% CT, 28% TT. Previous ancient DNA-based studies found that lactase persistence genotypes fall below detection levels in most regions of Neolithic Europe. Our research shows that by AD 1200, lactase persistence frequency had risen to over 70% in this community in western Central Europe. Given that lactase persistence genotype frequency in present-day Germany and Austria is estimated at 71-80%, our results suggest that genetic lactase persistence likely reached modern levels before the historic population declines associated with the Black Death, thus excluding plague-associated evolutionary forces in the rise of lactase persistence in this region. This new evidence sheds light on the dynamic evolutionary history of the European lactase persistence trait and its global cultural implications.

Full text, graphs, charts and 50 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3900515/

“The association of fructose and lactose intolerance and malabsorption with the symptoms of different functional gastrointestinal disorders remains unclear. Mechanisms relating to the generation of GI and non-GI symptoms due to lactose and fructose in functional gastrointestinal disorders need to be explored further.”

Alimentary Pharmacology And Therapy • June 2013

Fructose and lactose intolerance and malabsorption testing: the relationship with symptoms in functional gastrointestinal disorders

Author information

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Abstract

BACKGROUND
The association of fructose and lactose intolerance and malabsorption with the symptoms of different functional gastrointestinal disorders (FGID) remains unclear.

AIM
To investigate the prevalence of fructose and lactose intolerance (symptom induction) and malabsorption and their association with clinical gastrointestinal (GI) as well as non-GI symptoms in FGID and the outcome of dietary intervention.

METHODS
Fructose and lactose intolerance (defined by positive symptom index) and malabsorption (defined by increased hydrogen/methane) were determined in 1372 FGID patients in a single centre using breath testing. Results were correlated with clinical symptoms in different FGID Rome III subgroups. The effectiveness of a targeted saccharide-reduced diet was assessed after 6-8 weeks.

RESULTS
Intolerance prevalence across all FGIDs was 60% to fructose, 51% to lactose and 33% to both. Malabsorption occurred in 45%, 32% and 16% respectively. There were no differences in intolerance or malabsorption prevalence between FGID subgroups. FGID symptoms correlated with symptoms evoked during testing ($r = 0.35$-0.61. $P < 0.0001$), but not with malabsorption. Non-GI symptoms occurred more commonly in patients with intolerances. Methane breath levels were not associated with constipation using several cut-off thresholds. Adequate symptom relief was achieved in >80% of intolerant patients, irrespective of malabsorption.

CONCLUSIONS
Fructose and lactose intolerances are common in FGID and associated with increased non-GI symptoms, but not with specific FGID subtypes. Symptoms experienced during breath testing, but not malabsorption, correlate with FGID symptoms. Effective symptom relief with dietary adaptation is not associated with malabsorption. Mechanisms relating to the generation of GI and non-GI symptoms due to lactose and fructose in FGID need to be explored further.

Full text, graphs, charts and 53 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3672687/

“In young children with acute diarrhoea who are not predominantly breast-fed, change to a lactose-free diet may result in earlier resolution of acute diarrhoea and reduce treatment failure.”

Cochrane Database Of Systematic Reviews • October 2013

Lactose avoidance for young children with acute diarrhoea

Author information
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Abstract

BACKGROUND

Young children with acute diarrhoea, typically due to infectious gastroenteritis, may temporarily stop producing lactase, the intestinal enzyme that digests lactose. This means they may not digest lactose, the main sugar in milk, and this may worsen or prolong the diarrhoeal illness. However, there is uncertainty whether avoiding lactose-containing milk or milk products helps young children recover from acute diarrhoea more quickly.

OBJECTIVES

To assess if avoiding or reducing intake of lactose-containing milk or milk products shortens the duration and severity of illness in young children with acute diarrhoea. We also sought other indicators of morbidity and overall mortality.

SEARCH METHODS

We searched the Cochrane Infectious Diseases Group Specialized Register (14 May 2013), Cochrane Central Register of Controlled Trials (CENTRAL) published in The Cochrane Library (Issue 4, 2013), MEDLINE (1996 to 14 May 2013), EMBASE (1974 to 14 May 2013), and LILACS (1982 to 14 May 2013), and the reference lists of potentially relevant trials, key conference proceedings, and wrote to individuals and organizations in the field.

SELECTION CRITERIA

Randomized or quasi-randomized controlled trials that assessed the effects of avoiding or reducing exposure to lactose in young children under five years with acute diarrhoea.

DATA COLLECTION AND ANALYSIS

We extracted data using the standard methods of the Cochrane Infectious Diseases Group, and two review authors independently evaluated trial quality and data extraction. Continuous outcomes were compared using mean difference (MD), and dichotomous outcomes using the risk ratio (RR). We presented all results with 95% confidence intervals (CI) and assessed the quality of evidence using the GRADE approach.

MAIN RESULTS

We included 33 trials enrolling 2973 children with acute diarrhoea. Twenty-nine trials were exclusively conducted on inpatients, all from high- or middle-income countries. Fifteen trials included children aged below 12 months, and 22 excluded children who were being breast-fed.Compared to lactose-containing milk, milk products, or foodstuffs, lactose-free products may reduce the duration of diarrhoea by an average of about 18 hours (MD -17.77, 95% CI -25.32 to -10.21, 16 trials, 1467 participants, low quality evidence). Lactose-free products probably also reduce treatment failure (defined variously as continued or worsening diarrhoea or vomiting, the need for additional rehydration therapy, or continuing weight loss) by around a half (RR 0.52, 95% CI 0.39 to 0.68, 18 trials, 1470 participants, moderate quality evidence).Diluted lactose-containing milk has not been shown to reduce the duration of diarrhoea compared to undiluted milk or milk products (five trials, 417 participants, low quality evidence), but may reduce the risk of treatment failure (RR 0.65, 95% CI 0.45 to 0.94, nine trials, 687 participants, low quality evidence).

AUTHORS' CONCLUSIONS

In young children with acute diarrhoea who are not predominantly breast-fed, change to a lactose-free diet may result in earlier resolution of acute diarrhoea and reduce treatment failure. Diluting lactose-containing formulas may also have some benefits but further trials are required to have confidence in this finding. There are no trials from low-income countries, where mortality for diarrhoea is high, and malnutrition is more common.

http://www.ncbi.nlm.nih.gov/pubmed/24173771

Journal Of The American College Of Nutrition • October 2011

Milk and dairy products: a unique micronutrient combination

Author information

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Abstract

Milk and dairy products contain micronutrients such as minerals and vitamins, which contribute to multiple and different vital functions in the organism. The mineral fraction is composed of macroelements (Ca, Mg, Na, K, P, and Cl) and oligoelements (Fe, Cu, Zn, and Se). From a physicochemical point of view, the chemical forms, the associations with other ions or organic molecules, and the location of macroelements such as Ca, Mg, Na, K, P, and Cl in milk are relatively well described and understood. Thus, it is admitted that these macroelements are differently distributed into aqueous and micellar phases of milk, depending on their nature. K, Na, and Cl ions are essentially in the aqueous phase, whereas Ca, P, and Mg are partly bound to the casein micelles. About one third of the Ca, half of the P, and two thirds of the Mg are located in the aqueous phase of milk. Dairy products are more or less rich in these different minerals. In cheeses, mineral content depends mainly on their processing. The Ca content is strongly related to the acidification step. Moreover, if acidification is associated with the draining step, the Ca content in the cheese will be reduced. Thus, the Ca content varies in the following increasing order: milks/fermented milks/fresh cheeses < soft cheeses < semi-hard cheeses < hard cheeses. The chemical forms and associations are less described than those present in milk. Concerning Ca, the formation of insoluble calcium phosphate, carbonate, and lactate is reported in some ripened cheeses. The NaCl content in cheeses depends on the salting of the curd. From a nutritional point of view, it is largely admitted that milk and dairy products are important sources of Ca, Mg, Zn, and Se. The vitamin fraction of milk and dairy products is composed of lipophilic (A, D, E, and K) and hydrophilic (B(1), B(2), B(3), B(5), B(6), B(8), B(9), B(12), and C) vitamins. Because of their hydrophobic properties, the lipophilic vitamins are mainly in the milk fat fraction (cream, butter). The hydrophilic vitamins are in the aqueous phase of milk. For one part of these vitamins, the concentrations described in the literature are not always homogenous and sometimes not in accordance between them; these discrepancies are due to the difficulty of the sample preparation and the use of appropriate methods for their quantification. However, there is no doubt of the significant contribution of milk and dairy products to the intake of vitamins. Milk and dairy are considered essential sources for vitamins. Key teaching points: Milk and dairy products are unique micronutrient combinations with recognized health benefits. The concentration, chemical forms, and location of different minerals are relatively well known and described. For example, Ca is present in dairy products in different forms: free, associated with citrate, inorganic and organic phosphates, and free fatty acids. Milk and dairy products are excellent sources of Ca, P, Mg, Zn, and Se. The concentration of vitamins in milk and dairy products is variable and depends on several factors such as biosynthesis, animal feeding, physicochemical conditions (heat, light, O(2), oxidant agents), and analytical methods for their determinations. Vitamins A, D, E, and K are mainly located in the lipid phase and vitamins of group B and C in the aqueous phase. Milk and dairy products are excellent sources of vitamins A, B(1), B(2), and B(12).

http://www.ncbi.nlm.nih.gov/pubmed/22081685

London: RCOG Press Release • April 2009

Diarrhoea and Vomiting Caused by Gastroenteritis: Diagnosis, Assessment and Management in Children Younger than 5 Years

Editors: National Collaborating Centre for Women's and Children's Health (UK)
Source: National Institute for Health and Clinical Excellence

Excerpt

"When young children suddenly experience the onset of diarrhoea, with or without vomiting, infective gastroenteritis is by far the most common explanation. A range of enteric viruses, bacteria and protozoal pathogens may be responsible. Viral infections account for most cases in the developed world. Gastroenteritis is very common, with many infants and young children experiencing more than one episode in a year. The symptoms of gastroenteritis are unpleasant and the illness has an impact on both child and family. Vomiting causes distress and anxiety. Diarrhoea is often accompanied by abdominal pain. Infants and young children with severe symptoms may quickly become dehydrated. Dehydration is a serious and potentially life-threatening condition. The management of young children with gastroenteritis involves many considerations. Depending on the specific circumstances, care may be provided by parents or by a range of healthcare professionals. Children may be managed in a community or a hospital setting. There is debate and controversy regarding various aspects of clinical management. Clinical practice may have a major impact on the use of healthcare resources. Finally, there is evidence of considerable variation in practice in the management of children with gastroenteritis in the UK. It was for these reasons that this NICE clinical guideline on the 'management of acute diarrhoea and vomiting due to gastroenteritis in children under 5' was developed."

Full text, graphs, charts and 215 references

http://www.ncbi.nlm.nih.gov/books/NBK63844/pdf/Bookshelf_NBK63844.pdf

Annals In Allergy, Asthma And Immunology • August 2008

Incremental prognostic factors associated with cow's milk allergy outcomes in infant and child referrals: the Milan Cow's Milk Allergy Cohort study

Author information

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Abstract

BACKGROUND

The prognosis for many children with cow's milk allergy (CMA) is remission within 3 years, and the clinical parameters that predict duration of disease have not been measured incrementally.

OBJECTIVE

To prospectively determine prognostic predictors of tolerance in a random cohort of referrals using CMA workup outcomes as covariates and tolerance as the status variable in a duration model of CMA.

METHODS

The 2001-2006 Milan Cow's Milk Allergy Cohort (MiCMAC) enrolled children referrals using double-blind, placebo-controlled food challenges (DBPCFCs) as study end points (confirmation of CMA; onset of tolerance). The Cox regression model was used to analyze all clinical factors that contributed to tolerance. Covariates analyzed were skin, gastrointestinal, and respiratory symptoms; history and demographics at presentation; age at diagnosis and DBPCFC outcomes; sensitization (skin and serum) by cow's milk protein fractions; sensitization to other food and inhalant allergens; total IgE levels; specific IgE concentrations for cow's milk protein fractions, other ingestants, and aeroallergens; and threshold doses at DBPCFC. Sensitization and DBPCFC were performed at 6-month intervals.

RESULTS

A total of 112 infants were enrolled (mean [SD] age, 13.85 [9.84] months), and 59 achieved tolerance (mean [SD] age when tolerance was achieved, 27.58 [11.81] months). On univariate analysis, asthma and/or rhinitis at presentation was an independent predictor of persistence (hazard ratio [HR], 2.19; 95% confidence interval [CI], 1.26-3.82). On multivariate analysis, predictors of persistence were a fresh milk wheal diameter increment of 1 mm (HR, 1.18; 95% CI, 1.07-1.31) and a positive skin prick test result with soy (HR, 6.99; 95% CI, 1.56-31.25).

CONCLUSIONS

This is the first study, to our knowledge, to identify incremental biological predictors of delayed tolerance to cow's milk in children that should be integrated into DBPCFC schedules for CMA in infants.

http://www.ncbi.nlm.nih.gov/pubmed/18727472

“These results suggest that, starting as early as 10 years of age, self-imposed restriction of dairy foods because of perceived milk intolerance is associated with lower spinal bone mineral content values. The long-term influence of these behaviors may contribute to later risk for osteoporosis.”

Pediatrics • September 2007

Perceived milk intolerance is related to bone mineral content in 10- to 13-year-old female adolescents

Author information
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Abstract

OBJECTIVE

The purpose of this study was to determine associations among lactose maldigestion status, perceived milk intolerance, dietary calcium intake, and bone mineral content in early adolescent girls.

METHODS

Subjects were 291 girls who participated in a substudy of the multiple-site project Adequate Calcium Today. Lactose maldigestion status was determined with hydrogen breath testing, and questionnaires were used to assess perceived milk intolerance. Dietary calcium intake was estimated from a semiquantitative food frequency questionnaire. Anthropometric and dual-energy x-ray absorptiometric measurements (total body, spine L2-L4, total hip, and hip femoral neck) were standardized across sites.

RESULTS

Of the 230 girls who completed breath hydrogen testing, 65 were Asian, 76 were Hispanic, and 89 were non-Hispanic white. A total of 100 girls experienced increases in breath hydrogen levels of >20 ppm and were classified as lactose maldigesters. Of the 246 participants who completed useable perceived milk intolerance questionnaires, 47 considered themselves to be milk intolerant. Of the 47 girls self-reporting perceived milk intolerance, 40 completed breath hydrogen testing and 22 were not maldigesters. Girls with perceived milk intolerance consumed an average of 212 mg of total food calcium per day less than girls without perceived milk intolerance. Spinal bone mineral content was significantly lower in the girls with perceived milk intolerance, compared with the girls without perceived milk intolerance. When girls with lactose maldigestion were compared with girls without lactose maldigestion, there were no significant differences in calcium intake or bone measures.

CONCLUSIONS

These results suggest that, starting as early as 10 years of age, self-imposed restriction of dairy foods because of perceived milk intolerance is associated with lower spinal bone mineral content values. The long-term influence of these behaviors may contribute to later risk for osteoporosis.

http://www.ncbi.nlm.nih.gov/pubmed/17766507

Journal Of The American College Of Nutrition • December 2005

The myth of increased lactose intolerance in African-Americans

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Abstract

"In the United States, approximately three fourths of African-Americans have the potential for symptoms of lactose intolerance because lactose digestion depends on the presence of the enzyme lactase-phlorizin hydrolase which is reduced by up to 90-95% in individuals with lactase nonpersistence. The 'African-American diet' is more likely to be low in a variety of vitamins and minerals, including calcium. African-Americans consume low amounts of dairy foods and do not meet recommended intakes of a variety of vitamins and minerals, including calcium. Low intake of calcium and other nutrients put African-Americans at an increased risk for chronic diseases. The 2005 Dietary Guidelines recommend consuming three servings of dairy foods per day to ensure adequate calcium intake, among other nutrients, and the National Medical Association has recently published a similar recommendation of three to four servings of dairy per day for the African-American population. Research has shown that lactose maldigesters, including African-American maldigesters, can consume at least one cup (8 oz) of milk without experiencing symptoms, and that tolerance can be improved by consuming the milk with a meal, choosing yogurt or hard cheeses, or using products that aid in the digestion of lactose such as lactase supplements or lactose-reduced milks."

http://www.ncbi.nlm.nih.gov/pubmed/16373956

“In this study, lactose-free formula was shown to be effective in the dietary management of acute childhood diarrhea. Duration of diarrhea was shortened, weight gain was better, and stool frequency was less when compared to lactose-containing formula.”

Journal Of The Medical Association Of Thailand • June 2004

Randomized, double-blind clinical trial of a lactose-free and a lactose-containing formula in dietary management of acute childhood diarrhea

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Abstract

BACKGROUND

Refeeding of artificially fed infants with lactose-containing formula after oral rehydration therapy in the treatment of acute diarrhea was concluded to be indifferent to non-lactose formula by a meta-analysis. In Thai as well as Asian infants and children with low lactase level from genetically determinant and with rotavirus infection, lactose malabsorption is most likely to occur and cause delayed recovery. The aim of this study was to compare the effect of a lactose-free and a lactose-containing formula in dietary management of acute childhood diarrhea.

PATIENTS AND METHOD

A randomized, double-blind clinical trial of 80 male children, formula-fed, aged 3 to 24 months, admitted with acute watery diarrhea and mild or moderate dehydration, was carried out. All children received oral rehydration therapy for the first 4 hours. After appropriate rehydration, they were fed either a lactose-free formula (Dumex Lactose-Free Formula; treatment group, n = 40) or a lactose-containing formula (Dumex Infant Formula; control group, n = 40) in adjunction with oral rehydration solution. In addition, the infants were fed rice gruel as tolerated. Comparisons of duration of diarrhea, weight gain, vomiting, biochemical changes, stool frequency and weight and unscheduled intravenous fluid were made.

RESULTS

Three children (2 treatment, and 1 control) dropped out from the study. The total number of unscheduled intravenous infusions were 6 of 80 children (7.5%), including 2 (5.0%) in the treatment group and 4 (10.0%) in the control group. Three children in the control group did not resolve from diarrhea within 7 days of treatment. Rotavirus was identified in approximately 50% of the children in each group. Using survival analysis, the median duration of diarrhea was significantly shortened by 20.5 hours in the treatment group compared to the control group (77.0 hours in the treatment group vs 97.5 hours in the control group; P = 0.002). Significantly decrease in stool frequency and increase in percent weight gain were seen in the treatment group at 24 hours. Moderate acidosis cleared up to near normal at 24 hours in the treatment group but acidosis persisted in the control group. In the rotavirus diarrhea subgroup, moderate acidosis turned to be mild in treatment group, but acidosis was unchanged with increased plasma chloride level in the control at 24 hours thus suggesting that the children in the control group might have lactose malabsorption and osmotic diarrhea. Duration of rotavirus diarrhea was shortened 23.6 hours in treatment group compared to the control (P = 0.0034).

CONCLUSIONS

In this study, lactose-free formula was shown to be effective in the dietary management of acute childhood diarrhea. Duration of diarrhea was shortened, weight gain was better, and stool frequency was less when compared to lactose-containing formula. Moderate acidosis cleared up spontaneously at 24 hours. Unscheduled IV could be decreased by 50%. Children receiving lactose-free formula tolerated it well. Data of subgroup analysis of rotavirus diarrhea revealed lactose-free formula scored higher than the control group for all parameters studied.

http://www.ncbi.nlm.nih.gov/pubmed/15279342

Pediatrics Allergy And Immunology.• June 2004

Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention

Author information

By S. Halken

Abstract

The development and phenotypic expression of atopic diseases depends on a complex interaction between genetic factors, environmental exposure to allergens,and non-specific adjuvant factors, such as tobacco smoke, air pollution and infections. Preventive measures may include both exposure to allergens and adjuvant risk/protective factors and pharmacological treatment. These measures may address the general population, children at risk for development of atopic disease (high-risk infants), children with early symptoms of allergic disease or children with chronic disease. The objective for this review was to evaluate possible preventive measures as regards prevention of development of allergic disease in childhood--primary prevention--and also some aspects of the effect of specific allergy treatment as regards secondary prevention in children with allergic asthma and allergic rhinoconjunctivitis. In one prospective observational study of a birth cohort of unselected infants we evaluated possible predictive/risk factors. In two prospective intervention studies including 1 yr birth cohorts of high-risk(HR) infants we investigated the effect of feeding HR infants exclusively breast milk (BM) and/or hydrolyzed cow's milk-based formula the first 4-6 months as regards: (i) the allergy preventive effect of BM/extensively hydrolysed formula (eHF) compared with ordinary cow's milk-based formula, (ii) the effect of two different eHFs, a whey (Profylac) and a casein-based (Nutramigen) formula, as regards development of cow's milk protein allergy (CMA), and (iii) a comparison of the preventive effect of eHF (Profylac/Nutramigen) with a partially hydrolyzed cow's milk-based formula (pHF) (NanHA) as regards development of CMA. None of the mothers had a restricted diet during pregnancy or lactation period. In two prospective randomized intervention studies we evaluated the preventive effect of specific allergen avoidance and specific immunotherapy (SIT) in children with allergic asthma and allergic rhinoconjunctivitis, respectively. The combination of atopic heredity and elevated cord blood IgE resulted in the best predictive discrimination as regards development of allergic disease. The optimal high-risk group was defined by either double parental atopic predisposition or single atopic predisposition, the latter combined with a cord blood IgE > or = 0.3 kU/1. 66% of unselected infants were daily exposed to tobacco smoke, which was a significant risk factor for recurrent wheezing until the age of 1.5 yr. HR infants were breastfed for a longer period and less exposed to tobacco smoke than unselected infants. Exclusively BM/eHF for at least 4 months was associated with a significantly reduced cumulative prevalence of CMA [3.6% (5/141) vs. 20%(15/75) in the control group] up to 5 yr. The effect of the two different eHFs was similar. Exclusively breastfed infants were significantly less exposed to tobacco smoke and pets, had solid foods introduced later and belonged to higher social classes. pHF was significantly (p = 0.05) less effective than eHF as regards prevention of development of CMA. A diet period of 4 months seems to be as efficient as 6 months or more as regards development of CMA. A few ongoing prospective, randomized intervention studies have produced the first indication that avoidance of indoor allergens such as house dust mite (HDM) in HR infants may reduce the incidence of severe wheeze and sensitization during the first 1-4 yr of age. Long-term follow-up is awaited. In a prospective, double-blind placebo-controlled study in children with doctors diagnosed asthma and documented HDM allergy, we found that semipermeable polyurethane mattress and pillow encasings (Allergy Control) when compared with placebo encasings resulted in a significant perennial reduction of HDM exposure and a significant reduction in the needed dose of inhaled steroids by approximately 50% (mean dose: 408 microg--227 microg/day) after 1-yr follow-up. In another randomized prospective study we investigated the possible preventive effect of SIT in children with allergic rhinoconjunctivitis and grass/birch pollen allergy as regards development of asthma. Among those without asthma significantly fewer in the SIT group developed asthma when compared with the control group (19/79 = 24% vs.32/72 = 44%) after the first 3 yr; and methacholinebronchial provocation test results improved significant in the SIT group. The results of our studies support the evidence that the risk for development of early allergic manifestations e.g. CMA and atopic dermatitis can be reduced significantly by simple dietary measures for the first4 months of life. In all infants breastfeeding should be encouraged for at least 4-6 months, and exposure to tobacco smoke should be avoided during pregnancy and early childhood. In HR infants a documented hypoallergenic formula (at present eHF) is recommended if exclusive breastfeeding is not possible for the first 4 months. In homes of HR-infants, current evidence supports measures to reduce the levels of indoor allergens. e.g. HDM and pets. In symptomatic children allergen-specific treatment may influence both the symptoms and the prognosis. Allergen avoidance can reduce the need for pharmacological treatment, SIT may have the potential for preventing the development of asthma in children with allergic rhinoconjunctivitis. and it may be possible to interfere with the natural course of allergic diseases.

http://www.ncbi.nlm.nih.gov/pubmed/15125698

Allergy • August 2004

Hypoallergenic formulas—when, to whom and how long: after more than 15 years we know the right indication!

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Abstract

“Hypoallergenic formulas are processed by enzymatic hydrolysis of different protein sources such as bovine casein/whey and soy followed by further processing such as heat treatment and/or ultrafiltration, or they are based on amino acid mixtures. The products have been classified according to the degree of protein hydrolysis as ‘extensively’ or ‘partially’ hydrolysed protein products. Product properties may be characterized by biochemical techniques, and reduction of allergenicity may be assessed in vitro with various immunological methods, and in vivo with skin prick tests, patch tests and challenge tests. In vitro tests do not predict the allergenic effects in humans, and at present there is no evidence of a specific threshold of immunogenic protein. Only pure amino acid mixtures are considered to be nonallergenic. Other ‘hypoallergenic’ products contain residual allergenicity. At present, the potential of a product for treatment and prevention of food allergy can only be determined by clinical trials using scientifically appropriate standards. It has been recommended that dietary products for treatment of cow’s milk protein allergy in infants should be tolerated by at least 90% (with 95% confidence) of infants with documented cow’s milk protein allergy. Some extensively hydrolysed products and amino-acid-based products have met these criteria. Formulas intended for prevention should have a very low, if any, allergenic activity until otherwise proven. So far there are no firm criteria available for the design of hypoallergenic foods for prevention. Newborns included in prevention studies should be from high-risk families; they should be randomized at birth and fed the formula when supplements are needed for at least the first 4-6 months of life. Follow-up should be at least 18 months, and children should be investigated when symptoms appear. Validated clinical criteria, including controlled food challenges, should be used for diagnosis. Infants fed formulas that claim to prevent or delay allergy should have a statistically significant lower prevalence of allergy when compared with infants fed a standard cow’s milk formula. Feeding high-risk infants a documented hypoallergenic formula combined with avoidance of solid foods during the first 4-6 months reduces the cumulative incidence of cow’s milk protein allergy and atopic dermatitis as compared with a standard cow’s-milk-based formula. Partially hydrolysed formulas may have an effect, though it seems to be less than that of extensively hydrolysed formulas at present. Thus, if exclusive breast-feeding for 4-6 months is not possible in high-risk infants, a documented hypoallergenic formula and avoidance of solid foods are recommended for the first 4 months of life.”

Full text, graphs, charts and 55 references

http://onlinelibrary.wiley.com/doi/10.1046/j.1398-9995.2003.00387.x/epdf

“Because kefir improved lactose digestion and tolerance in this study, its use may be another potential strategy for overcoming lactose intolerance. Further studies of other types of kefir for improving lactose digestion are warranted.”

Journal Of The American Dieticians Association • May 2003

Kefir improves lactose digestion and tolerance in adults with lactose maldigestion

Author information
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Abstract

OBJECTIVE
Kefir is a fermented milk beverage that contains different cultures than yogurt. The objective of this study was to determine whether kefir improves lactose digestion and tolerance in adults with lactose maldigestion.

DESIGN
Randomized block design.

SUBJECTS
Fifteen healthy, free-living adults with lactose maldigestion.

MAIN OUTCOME MEASURES
Breath hydrogen excretion and lactose intolerance symptoms were monitored hourly for 8 hours after each test meal.

INTERVENTION
Subjects were fed test meals consisting of 20 g lactose portions of milk (2% reduced fat), plain and raspberry flavored kefir, and plain and raspberry flavored yogurt, each following an overnight (12 hour) fast.

STATISTICAL ANALYSIS
Mixed model ANOVA was performed on raw or transformed data, followed by Tukey HSD post hoc tests (when appropriate). Significance was defined as P<.05.

RESULTS
The breath hydrogen area under the curve (AUC) for milk (224+/-39 ppm x h) was significantly greater than for the plain yogurt (76+/-14 ppm x h, P<.001), the plain kefir (87+/-37 ppm x h, P<.001), and the flavored yogurt (76+/-14 ppm x h, P=.005). The flavored kefir had an intermediate response (156+/-26 ppm x h). The yogurts and kefirs all similarly reduced the perceived severity of flatulence by 54% to 71% relative to milk. Abdominal pain and diarrhea symptoms were negligible among the five treatments.

APPLICATIONS/CONCLUSION
Because kefir improved lactose digestion and tolerance in this study, its use may be another potential strategy for overcoming lactose intolerance. Further studies of other types of kefir for improving lactose digestion are warranted.

http://www.ncbi.nlm.nih.gov/pubmed/12728216

American Journal Of Clinical Nutrition • February 2001

Probiotics—compensation for lactase insufficiency

Author information
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Abstract

"Yogurt and other conventional starter cultures and probiotic bacteria in fermented and unfermented milk products improve lactose digestion and eliminate symptoms of intolerance in lactose maldigesters. These beneficial effects are due to microbial beta-galactosidase in the (fermented) milk product, delayed gastrointestinal transit, positive effects on intestinal functions and colonic microflora, and reduced sensitivity to symptoms. Intact bacterial cell walls, which act as a mechanical protection of lactase during gastric transit, and the release of the enzyme into the small intestine are determinants of efficiency. There is a poor correlation between lactose maldigestion and intolerance; in some studies, low hydrogen exhalation without significant improvement of clinical symptoms was observed. Probiotic bacteria, which by definition target the colon, normally promote lactose digestion in the small intestine less efficiently than do yogurt cultures. They may, however, alleviate clinical symptoms brought about by undigested lactose or other reasons."

Full text, graphs, charts and 53 references

http://ajcn.nutrition.org/content/73/2/421s.full.pdf

Journal Of The American Dieticians Association • May 2000

Improved lactose digestion and intolerance among African-American adolescent girls fed a dairy-rich diet

Author information
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Abstract

OBJECTIVE

To determine whether African-American adolescent girls who were fed a dairy-rich diet for 21 days could adapt to lactose, experiencing an overall improvement in lactose tolerance as well as a decrease in hydrogen gas production.

DESIGN

Twenty-one-day dietary intervention study.

SUBJECTS/SETTING

Seventeen of 21 African-American girls (aged 11 to 15 years) enrolled in a calcium metabolism study chose to participate in the lactose tolerance study. Subjects were screened for any diseases, conditions, or medications that might alter calcium metabolism or colonic fermentation. Subjects were housed in a fraternity on the Purdue University, West Lafayette, Ind, campus, and were supervised 24 hours a day.

INTERVENTION

Subjects consumed a dairy-based diet averaging 1,200 mg calcium and 33 g lactose per day for 21 days. Lactose digestion was assessed by an 8-hour breath hydrogen test on days 1 and 21, and symptoms of intolerance (abdominal pain, bloating, flatulence, and diarrhea) were evaluated hourly on a ranked scale during the breath hydrogen tests and once each evening during the 21-day feeding period.

MAIN OUTCOME MEASURES

A comparison of breath hydrogen production and gastrointestinal symptoms at the beginning and end of the study.

STATISTICAL ANALYSES PERFORMED

The Wilcoxon signed ranks test was used to compare the area under the curve for the 2 breath hydrogen tests. Spearman's p test for trend was used to determine whether there was a change in symptoms. All statistical analyses were 2-tailed and significance was set at P = .05.

RESULTS

Fourteen of the 17 subjects had lactose maldigestion. Breath hydrogen excretion decreased significantly ($P < .03$) from the beginning (148.3 +/- 27.0 ppm x hours) to the end (100.7 +/- 19.3 ppm x hours) of the 21-day period. Gastrointestinal symptoms were negligible during both the breath hydrogen tests as were symptoms during the 21-day period.

APPLICATIONS/CONCLUSIONS

The diet was well tolerated by the subjects. Furthermore, the decrease in breath hydrogen suggests colonic adaptation to the high-lactose diet. The results indicate that lactose maldigestion should not be a restricting factor in developing adequate calcium diets for this population. The existence of lactose maldigestion does not result in lactose intolerance in this population when it is fed a dairy-rich diet.

http://www.ncbi.nlm.nih.gov/pubmed/10812376

"The diet was well tolerated by the subjects. Furthermore, the decrease in breath hydrogen suggests colonic adaptation to the high-lactose diet. The results indicate that lactose maldigestion should not be a restricting factor in developing adequate calcium diets for this population. The existence of lactose maldigestion does not result in lactose intolerance in this population when it is fed a dairy-rich diet."

Allergy • June 2000

Evidence of very delayed clinical reactions to cow's milk in cow's milk-intolerant patients

Author information

Carroccio A1, Montalto G, Custro N, Notarbartolo A, Cavataio F, D'Amico D, Alabrese D, Iacono G.

Abstract

BACKGROUND

In patients with cow's milk protein intolerance (CMPI), delayed clinical reactions to cow's milk (CM) ingestion may be misdiagnosed if the clinical symptoms are not "classical" and there is a long time lapse between ingestion of CM and the clinical reaction. The aim was to evaluate the clinical outcome of CMPI in a cohort of CM-intolerant children, with particular attention to the occurrence of clinical manifestations beyond 72 h after CM challenge.

METHODS

Eighty-six consecutive patients (44 boys, 42 girls) with new CMPI diagnoses were enrolled; median age at diagnosis was 4 months. Patients were followed up for a mean period of 40 months. In all patients, CMPI diagnosis was made on the observation of symptoms, their disappearance after elimination diet, and their reappearance on double-blind CM challenge. At CMPI diagnosis, immunologic tests to demonstrate IgE-mediated hypersensitivity were performed. After 12 months of CM-free diet, CM tolerance was re-evaluated with a CM challenge continued at home for up to 30 days, according to a double-blind, placebo-controlled method. Patients who did not achieve CM tolerance continued a CM-free diet and subsequently underwent yearly CM challenge.

RESULTS

The percentages of CMPI patients who became CM-tolerant after 1, 2, and 3 years of CM-free diet were 30%, 54.5%, and 70%, respectively. At the end of the follow-up period, 26/86 subjects showed persistent CMPI; these patients had a higher percentage of positivity of total serum IgE ($P<0.05$), RAST ($P<0.01$), and cutaneous prick tests for CM antigens ($P<0.001$) than all the others. At CMPI diagnosis, all patients had a clinical reaction within 72 h from the beginning of the CM challenge; at the subsequent "cure" challenges, we observed patients who first reacted to CM more than 72 h after ingestion. In total, 10 out of 86 patients showed "very delayed reactions"; in these patients, the mean time between the beginning of CM challenge and the onset of a clinical symptom was 13.3 days (range 4-26 days). The number of "very late reactors" increased from the first to the third of the "cure" CM challenges, performed at yearly intervals. The "very delayed" CMPI manifestations in these subjects were constipation (five cases), wheezing (two cases), dermatitis plus constipation (two cases), and dermatitis alone (one case); in 6/10 patients, the symptoms observed at the "cure challenge" were different from those at CMPI onset.

CONCLUSIONS

Very delayed clinical reactions to reintroduction of CM in the diet can occur in CMPI patients; thus, accurate follow-up and frequent outpatient observation in patients with a long history of CMPI are probably more useful and safer than prolonged CM challenge.

http://www.ncbi.nlm.nih.gov/pubmed/10858991

"In patients with cow's milk protein intolerance (CMPI), delayed clinical reactions to cow's milk (CM) ingestion may be misdiagnosed if the clinical symptoms are not "classical" and there is a long time lapse between ingestion of CM and the clinical reaction. Very delayed clinical reactions to reintroduction of CM in the diet can occur in CMPI patients; thus, accurate follow-up and frequent outpatient observation in patients with a long history of CMPI are probably more useful and safer than prolonged CM challenge."

“In studies of the general population, the frequency of lactose intolerance is much lower than that of lactose maldigestion. Gastrointestinal symptoms after lactose load in self-reported milk-intolerants are found in only a very low number of these subjects. Furthermore, in these subjects we observed an unnecessary reduction in milk consumption and an insufficient dietary calcium intake.”

Journal Of The American College Of Nutrition • December 1998

Lactose intolerance and self-reported milk intolerance: relationship with lactose maldigestion and nutrient intake - Lactase Deficiency Study Group

Author information
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Abstract

BACKGROUND
The relationship between lactose-maldigestion, self-reported milk intolerance and gastrointestinal symptoms has not been clearly defined.

OBJECTIVES
To evaluate: a) the prevalence of lactose maldigestion and lactose intolerance in a sample of the general population taken from a rural center; b) the frequency of self-reported milk-intolerance and its correlation with lactose-maldigestion; c) the influence of lactose maldigestion, lactose intolerance and self-reported milk intolerance on dietary habits and consumption of total calories, protein, and calcium.

RESULTS
104/323 subjects (32.2%) were lactose maldigesters but tolerants, while 13/323 (4%) were lactose maldigesters and intolerants. In each age-class group (pediatric, adult, and elderly subjects) only the lactose maldigester and intolerant subjects showed differences in nutrient intake with a significantly lower daily consumption of milk and a lower calcium intake. 49/323 subjects were self-reported milk-intolerants; of these, 26 (53%) were lactose maldigesters but tolerants, 18 (37%) were lactose digesters and tolerants and only 5 (10%) were lactose maldigesters and intolerants. In the whole group of self-reported milk-intolerants, dietary milk consumption was significantly reduced and calcium intake was lower than in all the other subjects studied (320 mg/day vs. 585 mg/day, $p<0.05$).

CONCLUSIONS
In studies of the general population, the frequency of lactose intolerance is much lower than that of lactose maldigestion. Gastrointestinal symptoms after lactose load in self-reported milk-intolerants are found in only a very low number of these subjects. Furthermore, in these subjects we observed an unnecessary reduction in milk consumption and an insufficient dietary calcium intake.

http://www.ncbi.nlm.nih.gov/pubmed/9853544

Clinical And Experimental Allergy • March 1996

Distinct patterns of cow's milk allergy in infancy defined by prolonged, two-stage double-blind, placebo-controlled food challenges

Author information

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Abstract

BACKGROUND

The clinical manifestations of cow's milk allergy (CMA) are highly variable, and challenges usually identify only immediate, IgE mediated reactions.

OBJECTIVE

To clearly identify CMA of immediate and delayed types using a two-stage, double-blind, placebo-controlled food challenge (DBPCFC), and to prospectively compare the clinical history and analyses of specific IgE antibodies to milk in predicting outcome of DBPCFC.

METHODS

A total of 69 patients (33 girls, 36 boys) were recruited for study based on a history highly suggestive of CMA and resolution of symptoms on a bovine protein-free diet. After skin-prick tests (SPTs) and search for allergen-specific serum IgE antibodies by enzyme allergosorbent test (EAST), a two-stage DBPCFC was performed over several days.

RESULTS

Of 16 patients (mean age 36.9 months) classified as probable immediate reactors based on the history, 10 (62.5%) had a positive DBPCFC with similar patterns to historical adverse reactions (< or = 2 h after milk exposure). The other 53 (77%) patients (17.3 months) had a history of probable delayed type CMA presenting with predominantly gastrointestimal symptoms from 2 h and up to 6 days after milk exposure. Of these, 15 (28.8%) had a positive DBPCFC, again with a symptom pattern similar to the history. Sensitivity/specificity of SPT was similar to that of EAST for both immediate (70/83% and 62/83% respectively, NS) or delayed (0/97% and 0/97%) CMA confirmed by DBPCFC.

CONCLUSIONS

Using our two-stage, prolonged DBPCFC, we clearly identified two groups of children with CMA, reflecting different pathogenesis of either immediate-type IgE-dependent, or delayed-type IgE-independent allergy. Although useful in immediate reactors, IgE antibody determination cannot predict the outcome of DBPCFC in delayed reactors. A thorough clinical history was the most helpful tool to predict the type of response in challenge positive patients.

http://www.ncbi.nlm.nih.gov/pubmed/8729661

European Journal Of Clinical Nutrition • September 1995

The natural history of cow's milk protein allergy/intolerance

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Abstract

In prospective studies th incidence of cow's milk protein allergy and intolerance (CMPA/CMPI) in infancy in western industrialized countries has been estimated to be about 2-3% based on strict diagnostic criteria. A significant association between early neonatal exposure to cow's milk formula feeding and subsequent development of CMPA/CMPI has been documented. The small amounts of 'foreign' protein in human milk may rather induce tolerance than allergic sensitization. The findings of specific IgE to individual cow's milk proteins in cord blood of the majority of infants who later develop CMPA/CMPI suggests a prenatal sensitization may play a role in the pathogenesis of CMPA/CMPI. Perhaps a weak intrauterine education of low IgE-response may need to 'boosted' neonatally in order to cause clinical disease. The prognosis of CMPA/CMPI is good with a recovery of about 45-56% at one year, 60-77% at two years and 71-87% at three years. Associated adverse reactions to other foods, especially egg, soy, peanut and citrus develop in about 41-54%. Allergy to potential environmental inhalant allergens has been reported in up to 28% by three years and up to 80% before the age of puberty. Especially, infants with an early increased IgE response to cow's milk protein have an increased risk of persisting CMPA, development of persistent adverse reactions to other foods and development of allergy against environmental inhalant allergens. Cow's milk protein/intolerance (CMPA/CMPI), meaning reproducible adverse reactions to cow's milk protein(s) may be due to the interaction between one or more milk proteins and one or more immune mechanisms, possible any of the four basic types of hypersensitivity reactions. Immunologically mediated reactions are defined as CMPA. Mostly, CMPA is caused by IgE-mediated (type I) reactions, but evidence for type III (immune complex) reactions and type IV (cell mediated reactions) have been demonstrated as reviewed by Høst (1994) and Ortolani & Vighi (1995). Non immunologically reactions against cow's milk protein(s) are defined as CMPI. However, it should be stressed that many studies on 'cow's milk allergy' have not investigated the immunological basis of the clinical reactions. In most instances of cow's milk protein hypersensitivity only diagnostic investigations such as skin prick test and RAST indicative of IgE-mediated reactions are performed. In fact, CMPA cannot be ruled out unless extensive diagnostic tests for type II-III-IV reactions have proved negative. Thus, the classification of adverse reactions to cow's milk proteins depends on the extent and the quality of performed diagnostic tests for immune mediated reactions. At present, no single laboratory test is diagnostic of CMPA/CMPI, and differentiation between CMPA and CMPI cannot be based solely on clinical symptoms. Therefore the diagnosis has to be based on strict well-defined elimination and milk challenge procedure (Hill & Hosking, 1991), (Høst, 1994). Preferably, double-blind placebo-controlled challenges (DBPCFC) should be carried out in children older than 1-2 years of age. In infants open controlled challenges have been shown to be reliable when performed under professional observation in a hospital setting (Høst & Halken, 1990).

http://www.ncbi.nlm.nih.gov/pubmed/8647059

CHAPTER FORTY-THREE

Thaumatin

The Peer Review

Thaumatin is a low-calorie sweetener and flavor modifier. The protein can only be legally used in the US for its flavor-modifying properties and not exclusively as a sweetener. The thaumatins were first found as a mixture of proteins isolated from the katemfe fruit of west Africa. Some proteins in the thaumatin family of sweeteners are roughly 2000 times more potent than sugar. Although very sweet, thaumatin's taste is markedly different from sugar's. The sweetness of thaumatin builds very slowly. Perception lasts a long time, leaving a liquorice-like aftertaste at high usage levels. Thaumatin is highly water-soluble, stable to heating, and stable under acidic conditions.

Thaumatin production is induced in katemfe in response to an attack upon the plant by viroid pathogens. Several members of the thaumatin protein family display significant in vitro inhibition of hyphal growth and sporulation by various fungi. The thaumatin protein is considered a prototype for a pathogen-response protein domain. This thaumatin domain has been found in species as diverse as rice and Caenorhabditis elegans. Thaumatins are pathogenesis-related (PR) proteins, which are induced by various agents ranging from ethylene to pathogens, and are structurally diverse and ubiquitous in plants: They include thaumatin, osmotin, tobacco major and minor PR proteins, alpha-amylase/trypsin inhibitor, and P21 and PWIR2 soybean and wheat leaf proteins. The proteins are involved in systematically acquired resistance and stress response in plants, although their precise role is unknown. Thaumatin is an intensely sweet-tasting protein (on a molar basis about 100,000 times as sweet as sucrose) found in the West African shrub Thaumatococcus daniellii: it is induced by attack by viroids, which are single-stranded unencapsulated RNA molecules that do not code for protein. The thaumatin protein I consists of a single polypeptide chain of 207 residues. Like other PR proteins, thaumatin is predicted to have a mainly beta structure, with a high content of beta-turns and little helix. Tobacco cells exposed to gradually increased salt concentrations develop a greatly increased tolerance to salt, due to the expression of osmotin, a member of the PR protein family. Wheat plants attacked by barley powdery mildew express a PR protein (PWIR2), which results in resistance against that infection. The similarity between this PR protein and other PR proteins to the maize alpha-amylase/trypsin inhibitor has suggested PR proteins may act as some form of inhibitor. The thaumatin-like proteins isolated from kiwi fruit or apple appear to have their allergenic properties minimally reduced by gastroduodenal digestive processes, but not by heating.

Within West Africa, the katemfe fruit has been locally cultivated and used to flavor foods and beverages for some time. The fruit's seeds are encased in a membranous sac, or aril, that is the source of thaumatin. In the 1970s, Tate and Lyle began extracting thaumatin from the fruit. In 1990, researchers at Unilever reported the isolation and sequencing of the two principal proteins found in thaumatin, which they dubbed thaumatin I and thaumatin II. These researchers were also able to express thaumatin in genetically engineered bacteria. Thaumatin has been approved as a sweetener in the European Union (E957), Israel, and Japan. In the United States, it is generally recognized as safe as a flavoring agent (FEMA GRAS 3732) but not as a sweetener. Thaumatin can be listed as a 'natural flavor' on food labels.

Plant Physiology • January 2016

Rj4, a Gene Controlling Nodulation Specificity in Soybeans, Encodes a Thaumatin-Like Protein But Not the One Previously Reported

Tang F1, Yang S1, Liu J1, Zhu H2.

Abstract

"Rj4 is a dominant gene in soybeans (Glycine max) that restricts nodulation by many strains of Bradyrhizobium elkanii. The soybean-B. elkanii symbiosis has a low nitrogen-fixation efficiency, but B. elkanii strains are highly competitive for nodulation; thus, cultivars harboring an Rj4 allele are considered favorable. Cloning the Rj4 gene is the first step in understanding the molecular basis of Rj4-mediated nodulation restriction and facilitates the development of molecular tools for genetic improvement of nitrogen fixation in soybeans. We finely mapped the Rj4 locus within a small genomic region on soybean chromosome 1, and validated one of the candidate genes as Rj4 using both complementation tests and CRISPR/Cas9-based gene knockout experiments. We demonstrated that Rj4 encodes a thaumatin-like protein, for which a corresponding allele is not present in the surveyed rj4 genotypes, including the reference genome Williams 82. Our conclusion disagrees with the previous report that Rj4 is the Glyma.01G165800 gene (previously annotated as Glyma01g37060). Instead, we provide convincing evidence that Rj4 is Glyma.01g165800-D, a duplicated and unique version of Glyma.01g165800, that has evolved the ability to control symbiotic specificity."

http://www.ncbi.nlm.nih.gov/pubmed/26582727

“Thaumatin is an intensely sweet-tasting protein that elicits sweet taste at a concentration of 50 nM, a value 100,000 times larger than that of sucrose ... These findings clearly confirm the importance of electrostatic potentials in the interaction of thaumatin with the sweet receptor.”

Science Reports • February 2016

A Hypersweet Protein: Removal of The Specific Negative Charge at Asp21 Enhances Thaumatin Sweetness

Author information

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Abstract

Thaumatin is an intensely sweet-tasting protein that elicits sweet taste at a concentration of 50 nM, a value 100,000 times larger than that of sucrose on a molar basis. Here we attempted to produce a protein with enhanced sweetness by removing negative charges on the interacting side of thaumatin with the taste receptor. We obtained a D21N mutant which, with a threshold value 31 nM is much sweeter than wild type thaumatin and, together with the Y65R mutant of single chain monellin, one of the two sweetest proteins known so far. The complex model between the T1R2-T1R3 sweet receptor and thaumatin, derived from tethered docking in the framework of the wedge model, confirmed that each of the positively charged residues critical for sweetness is close to a receptor residue of opposite charge to yield optimal electrostatic interaction. Furthermore, the distance between D21 and its possible counterpart D433 (located on the T1R2 protomer of the receptor) is safely large to avoid electrostatic repulsion but, at the same time, amenable to a closer approach if D21 is mutated into the corresponding asparagine. These findings clearly confirm the importance of electrostatic potentials in the interaction of thaumatin with the sweet receptor.

Full text, graphs, charts and 52 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4738316/

“Plant[s] often responds to fungal pathogens by expressing a group of proteins known as pathogenesis-related proteins (PRs) ... expression of the defense marker genes suggested up-regulation of the defense-response pathways in ObTLP1-expressing Arabidopsis upon fungal challenge. Thus, ObTLP1 might be useful for providing tolerance to the fungal pathogens and abiotic stresses in crops.”

Science Reports • May 2016

A thaumatin-like protein of Ocimum basilicum confers tolerance to fungal pathogen and abiotic stress in transgenic Arabidopsis

Author information

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Abstract

Plant often responds to fungal pathogens by expressing a group of proteins known as pathogenesis-related proteins (PRs). The expression of PR is mediated through pathogen-induced signal-transduction pathways that are fine-tuned by phytohormones such as methyl jasmonate (MeJA). Here, we report functional characterization of an Ocimum basilicum PR5 family member (ObTLP1) that was identified from a MeJA-responsive expression sequence tag collection. ObTLP1 encodes a 226 amino acid polypeptide that showed sequence and structural similarities with a sweet-tasting protein thaumatin of Thaumatococcus danielli and also with a stress-responsive protein osmotin of Nicotiana tabacum. The expression of ObTLP1 in O. basilicum was found to be organ-preferential under unstressed condition, and responsive to biotic and abiotic stresses, and multiple phytohormone elicitations. Bacterially-expressed recombinant ObTLP1 inhibited mycelial growth of the phytopathogenic fungi, Scleretonia sclerotiorum and Botrytis cinerea; thereby, suggesting its antifungal activity. Ectopic expression of ObTLP1 in Arabidopsis led to enhanced tolerance to S. sclerotiorum and B. cinerea infections, and also to dehydration and salt stress. Moreover, induced expression of the defense marker genes suggested up-regulation of the defense-response pathways in ObTLP1-expressing Arabidopsis upon fungal challenge. Thus, ObTLP1 might be useful for providing tolerance to the fungal pathogens and abiotic stresses in crops.

Full text, graphs, charts and 59 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4858651/

Food Chemistry • June 2016

Influence of polysaccharides on wine protein aggregation

Author information

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Abstract

“Polysaccharides are the major high-molecular weight components of wines. In contrast, proteins occur only in small amounts in wine, but contribute to haze formation. The detailed mechanism of aggregation of these proteins, especially in combination with other wine components, remains unclear. This study demonstrates the different aggregation behavior between a buffer and a model wine system by dynamic light scattering. Arabinogalactan-protein, for example, shows an increased aggregation in the model wine system, while in the buffer system a reducing effect is observed. Thus, we could show the importance to examine the behavior of wine additives under conditions close to reality, instead of simpler buffer systems. Additional experiments on melting points of wine proteins reveal that only some isoforms of thaumatin-like proteins and chitinases are involved in haze formation. We can confirm interactions between polysaccharides and proteins, but none of these polysaccharides is able to prevent haze in wine.”

http://www.ncbi.nlm.nih.gov/pubmed/26830558

“These results demonstrate the potential of an expression system based on transgenic tomato plants for production of recombinant thaumatin for the food and pharmaceutical industries.”

Protein Expression And Purification • July 2016

Purification and characterization of recombinant supersweet protein thaumatin II from tomato fruit

Author information

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Abstract

Thaumatin, a supersweet protein from the African plant katemfe (Thaumatococcus daniellii Benth.), is a promising zero-calorie sweetener for use in the food and pharmaceutical industries. Due to limited natural sources of thaumatin, its production using transgenic plants is an advantageous alternative. We report a simple protocol for purification of recombinant thaumatin II from transgenic tomato. Thaumatin was extracted from ripe tomato fruit in a low-salt buffer and purified on an SP-Sephacryl column. Recombinant thaumatin yield averaged 50 mg/kg fresh fruit. MALDI-MS analysis showed correct processing of thaumatin in tomato plants. The recombinant thaumatin was indistinguishable from the native protein in a taste test. The purified tomato-derived thaumatin had an intrinsic sweetness with a threshold value in taste tests of around 50 nM. These results demonstrate the potential of an expression system based on transgenic tomato plants for production of recombinant thaumatin for the food and pharmaceutical industries.

http://www.ncbi.nlm.nih.gov/pubmed/26965414

Rocz Panstw Zakl Hig 2015;66(3):195-202

http://wydawnictwa.pzh.gov.pl/roczniki_pzh/

REVIEW ARTICLE

NATURAL SWEETENERS IN A HUMAN DIET

*Małgorzata Grembecka**

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ABSTRACT

Sweeteners, both natural and artificial, play an important role in a human diet as well as are of great importance to the food industry and dieticians. Many people associate sweet taste with sucrose, which is commonly known as table sugar. However, there are many sweet substances that food manufacturers add to food products because none of them is ideal for all applications. Besides sucrose there are also other sugars such as glucose and fructose that originate both from natural sources such as fruits and honey or from added sugars. Among sweeteners there are also compounds which have a sweet taste and contain no calories or those which sweetness is so intense so can be used at very low concentrations, thus, their impact on the total caloric value of the product is negligible. They can be classified due to their origin (natural or synthetic agents), the technological function (sweeteners and fillers), texture (powders and syrups), and nutritional value (caloric and non-caloric). Natural sweetening substances include carbohydrates, sugar alcohols, thaumatin and stevia. Besides providing well tasting foods, they might have an impact on products' texture, color, preservation and caloric value. Sugar alcohols, which belong to carbohydrates, are both natural sugar substitutes and food additives. They are becoming more and more popular among consumers mainly due to their lower caloric values and glycemic indexes as well as anticariogenic effects. Sugar alcohols are often combined with other sweeteners to enhance food products' sweetness. Stevia, which is 200 times sweeter than sucrose, is a non caloric substance whereas thaumatin, a sweet protein, provides 4 kcal/g but characterizes with sweetness about 2000 times higher than sucrose (on a weight basis).

Key words: *sweeteners, added sugars, sugar alcohols, stevia, thaumatin*

http://www.ncbi.nlm.nih.gov/pubmed/26400114

Full text with 65 references

Click the "Full Text Link" at the top right-hand side of the page

“The unique intense sweet-taste of thaumatin might be attributed to the different receptor activation mechanism compared to the small molecule sweetener sucralose.”

Biochimie • July 2013

Five amino acid residues in cysteine-rich domain of human T1R3 were involved in the response for sweet-tasting protein, thaumatin

Author information

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Abstract

Thaumatin, a sweet-tasting plant protein, elicits a sweet taste sensation at 50 nM in humans but not rodents. Although it was shown that the cysteine-rich domain (CRD) of human T1R3 (hT1R3) is important for the response to thaumatin, the amino acid residues within CRD critical for response are still unknown. A comparison of the amino acid sequence (69 amino acid residues) of CRD between hT1R3 and mouse T1R3 (mT1R3) revealed sixteen amino acids that differ. In the present study, we converted each of these sixteen amino acids in hT1R3 to their mouse counterpart and examined the response to thaumatin and sucralose using a cell-based assay. No significant decrease in the response to sucralose was seen among any of the sixteen mutants. However, five mutants (Q504K, A537T, R556P, S559P, and R560K) exhibited a significantly diminished response to thaumatin. The five critical residues involved in the response to thaumatin were dispersed in the CRD of hT1R3 and widely distributed when compared to brazzein. The unique intense sweet-taste of thaumatin might be attributed to the different receptor activation mechanism compared to the small molecule sweetener sucralose.

http://www.ncbi.nlm.nih.gov/pubmed/23370115

“This gives a promising opportunity to explore this protein for potential health application in the low calorie sweetener industry viz., soft drinks, snacks, food, chocolate industries etc.”

Bioinformation • September 2011

Identification of novel sweet protein for nutritional applications

Author information

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Abstract

The prevalence of obesity and diabetes has increased exponentially in recent years around the globe, especially in India. Sweet proteins have the potential to substitute the sugars, by acting as natural, good and low calorie sweeteners. They also do not trigger a demand for insulin in diabetic patients unlike sucrose. In humans, the sweet taste perception is mainly due to taste-specific G protein-coupled heterodimeric receptors T1R2-T1R3. These receptors recognize diverse natural and synthetic sweeteners such as monelin, brazzein, thaumatin, curculin, mabinlin, miraculin and pentadin. Structural modeling of new sweetener proteins will be a great leap in further advancement of knowledge and their utility as sweeteners. We have explored the fingerprints of sweetness by studying the aminoacid composition and structure properties of the above proteins. The structural analysis of monellin revealed that the individual A or B chains of monellin are not contributing to its sweetness. However, the native conformation and ionic interaction between AspB7 of monellin with active site of T1R2-T1R3 receptor, along with hydrogen bonding stability of IleB6 and IleB8 are responsible for the sweet taste. Based on structural similarity search, we found a new hypothetical protein from Shewanella loihica, which has the presence of Asp(32) with adjacent isoleucine residues. Further, we examined the lead protein by two-step docking for the study of interaction of functionally conserved residues with receptors. The identified protein showed similar ionic and hydrophobic interactions with monelin. This gives a promising opportunity to explore this protein for potential health application in the low calorie sweetener industry viz., soft drinks, snacks, food, chocolate industries etc.

Full text, photos, graphs, charts and 12 references

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3218311/

FEBS Journal • July 2008

Critical molecular regions for elicitation of the sweetness of the sweet-tasting protein, thaumatin I

Author information
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Abstract

“Thaumatin is an intensely sweet-tasting protein. To identify the critical amino acid residue(s) responsible for elicitation of the sweetness of thaumatin, we prepared mutant thaumatin proteins, using Pichia pastoris, in which alanine residues were substituted for lysine or arginine residues, and the sweetness of each mutant protein was evaluated by sensory analysis in humans. Four lysine residues (K49, K67, K106 and K163) and three arginine residues (R76, R79 and R82) played significant roles in thaumatin sweetness. Of these residues, K67 and R82 were particularly important for eliciting the sweetness. We also prepared two further mutant thaumatin I proteins: one in which an arginine residue was substituted for a lysine residue, R82K, and one in which a lysine residue was substituted for an arginine residue, K67R. The threshold value for sweetness was higher for R82K than for thaumatin I, indicating that not only the positive charge but also the structure of the side chain of the arginine residue at position 82 influences the sweetness of thaumatin, whereas only the positive charge of the K67 side chain affects sweetness.”

http://www.ncbi.nlm.nih.gov/pubmed/18544096

Chemical Senses • February 2001

Structure-sweetness relationship in thaumatin: importance of lysine residues

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Abstract

“To clarify the structural basis for the sweetness of thaumatin I, lysine-modified derivatives and carboxyl-group-modified derivatives were prepared by chemical modification followed by chromatographic purification. The sweetness of derivatives was evaluated by sensory analysis. Phosphopyridoxylation of lysine residues Lys78, Lys97, Lys106, Lys137 and Lys187 markedly reduced sweetness. The intensity of sweetness was returned to that of native thaumatin by dephosphorylation of these phosphopyridoxylated lysine residues except Lys106. Pyridoxamine modification of the carboxyl group of Asp21, Glu42, Asp60, Asp129 or Ala207 (C-terminal) did not markedly change sweetness. Analysis by far-UV circular dichroism spectroscopy indicated that the secondary structure of all derivatives remained unchanged, suggesting that the loss of sweetness was not a result of major disruption in protein structure. The five lysine residues, modification of which affected sweetness, are separate and spread over a broad surface region on one side of the thaumatin I molecule. These lysine residues exist in thaumatin, but not in non-sweet thaumatin-like proteins, suggesting that these lysine residues are required for sweetness. These lysine residues may play an important role in sweetness through a multipoint interaction with a putative thaumatin receptor.”

Full text with 44 references

http://chemse.oxfordjournals.org/content/26/2/167.long

END

I hope the reader has learned from this eBook that these additives are all drugs.
They have no business in our food. We know very little about them yet what we do know is frightening.
I hope that you'll consider synergy and how the various chemicals we encounter each day may affect us in combination.
I hope you avoid these chemicals and others because you'll live longer and you'll live healthier.

NOTES

GRAS Notices

http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices

Food Ingredient and Packaging Inventories

http://www.fda.gov/Food/IngredientsPackagingLabeling/ucm112642.htm

GRAS Notice Inventory

The inventory of GRAS notices provides the following information about GRAS notices filed within each year since 1998, when FDA received its first GRAS notice:

- The name of the substance
- The file number (GRN No.) that FDA has assigned to the notice
- A hyperlink to the letter that FDA sent in response to the notice.
  The text of this link also indicates the date of the letter.

The file number for each GRAS notice also serves as a hyperlink to additional information corresponding to the proposed "GRAS exemption claim" (proposed 21 CFR 170.36(c)(1)), including the following information, which FDA proposed to make readily accessible to the public:

- The name of the person who made the GRAS determination (notifier)
- The notifier's address
- The intended conditions of use of the substance
- The statutory basis for the GRAS determination

Additional information includes:

- The date when FDA filed the notice
- The date when the evaluation process came to closure
- When applicable, a hyperlink to additional correspondence that FDA has issued regarding the GRAS notice
- The petition number if the substance was originally the subject of a GRAS petition
- In some cases, a hyperlink to the notice itself

Persons interested in obtaining additional data and information in the notice may obtain a copy of those data and information that are disclosable by requesting the information under the Freedom of Information Act. We will update this information approximately monthly.

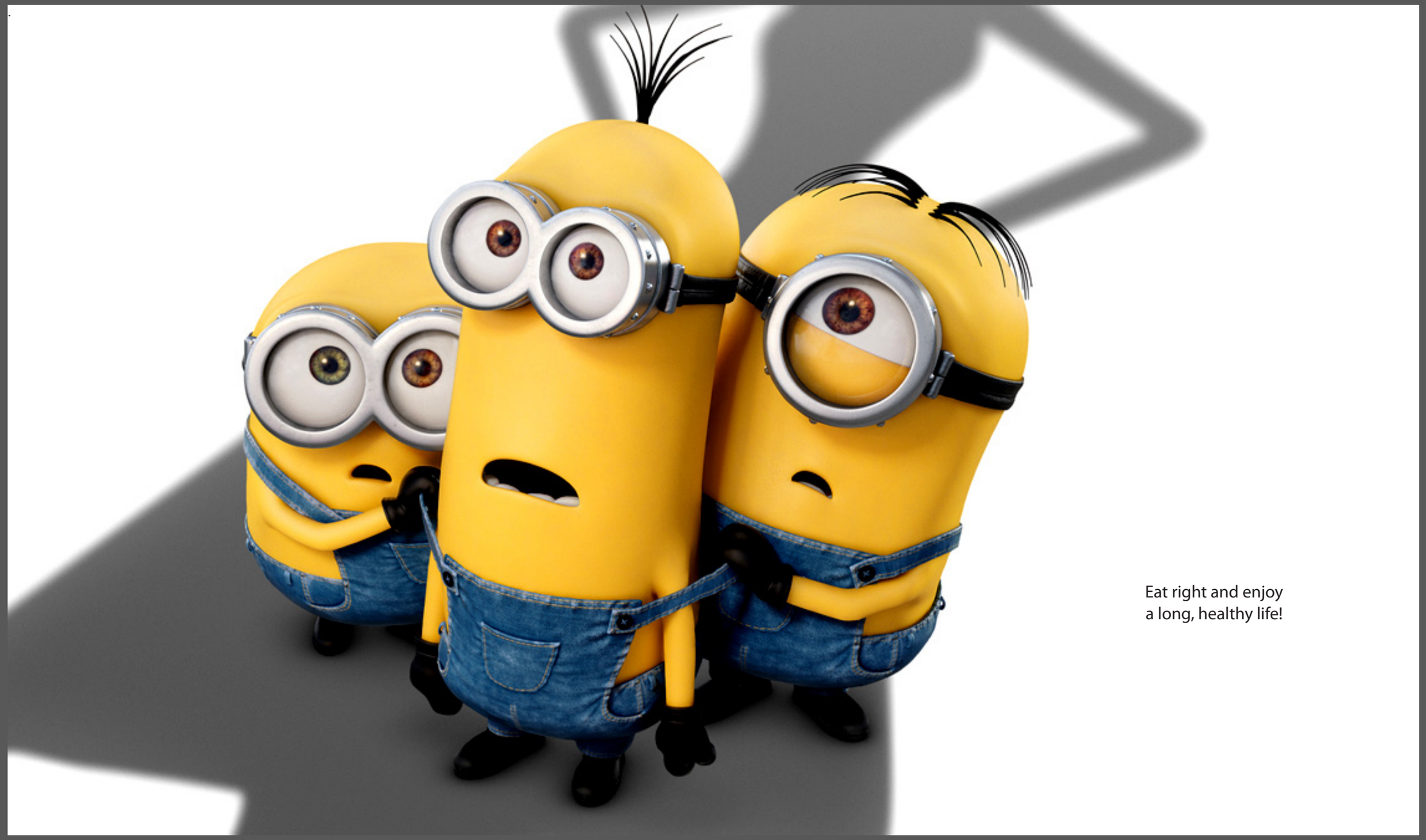
http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm

Food Additives and Ingredients

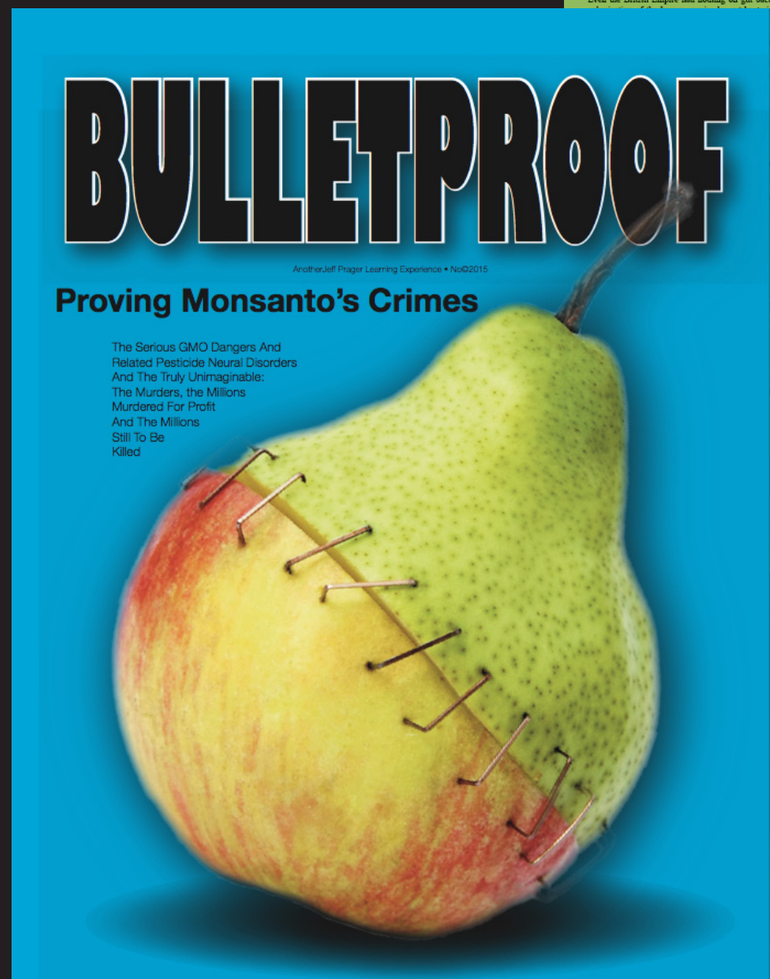
http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/default.htm

Everything Added To Food In The United States

http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm115326.htm



Eat right and enjoy
a long, healthy life!



Silent Partners

Over 7 Billion Humans Have Been Colonized By Bacteria - Not A Shot Fired

by Jeff Prager

Even the British Empire had nothing on gut bacteria. The successful [illegible] is a largely untold [illegible]sire to simply live. [illegible]t number of bacteria [illegible]h. Factually, from a [illegible]emain alive without [illegible]h over 400 different [illegible]*but we'll stick to the* [illegible]n the digestive tract. [illegible]od health and others [illegible]e they actively assist

[illegible]cteria

[illegible]lly bacteria in the up- [illegible]harmful bacteria and [illegible]tase, an enzyme im- [illegible] involved in the pro-

[illegible]mary friendly bacte- [illegible] large intestine from [illegible] B vitamins and help [illegible]he prevalent friendly

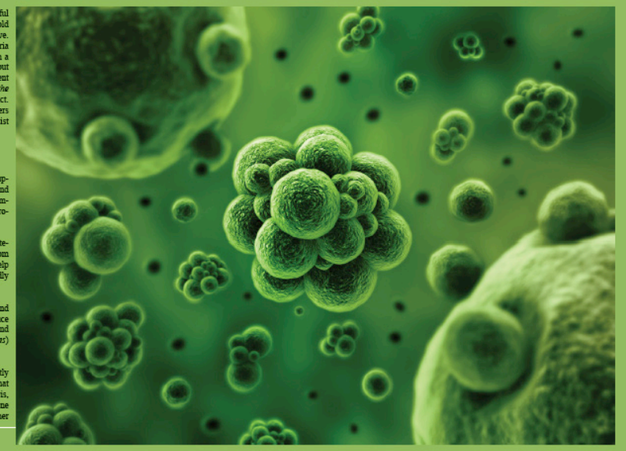
[illegible]ost commonly found [illegible] tract. They produce [illegible]friendly bacteria, and [illegible]*tics like substances*)

[illegible] the bacteria mostly [illegible]eneficial species that [illegible]oregenes, L. brevis, [illegible]ke acidophilus, one [illegible]b vitamins and other

[illegible] of us. But it can turn rogue, causing skin infections—or worse. [illegible] century has prompted the evolution of deadly superbug strains. [illegible]erium that is a member of the Firmicutes, and is frequently found [illegible]sitive for catalase and nitrate reduction. Although S. aureus is not [illegible]ctious (e.g. boils), respiratory disease (e.g. sinusitis), and food poisoning. Disease-associated strains often promote infections by producing potent protein toxins, and expressing cell-surface proteins that bind and inactivate antibodies. The emergence of antibiotic-resistant forms of pathogenic S. aureus (e.g. MRSA) is a worldwide problem in clinical medicine.

The Benefits Of Probiotics

We don't even know if probiotics work. We don't know if they manufacture our needed B vitamins, including niacin, pyridoxine, folic acid, and biotin. We don't know if they enhance our immune system activity. We don't know if antibacterial substances that kill or deactivate hostile disease causing bacteria actually work at all. Friendly bacteria do this by changing the local levels of acidity, by depriving pathogenic bacteria of their nutrients, or by actually producing their own antibiotic substances, yet we don't know if drinking kefir, eating pickles and sauerkraut or ingesting probiotics even works. We don't know if the ingested bacteria builds a house on your intestinal wall, so to speak, and lives in your gut for a day, a week, a month or forever or whether they take the next gut-wrenching feces train to Sewer City, USA on the Toilet Express. Honestly, we're clueless. But we think it helps.



Gut Bacteria

by Jeff Prager

Gut microorganisms benefit the host by gleaning the energy from the fermentation of undigested carbohydrates and the subsequent absorption of short-chain fatty acids. The most important of these fatty acids are:

- Butyrates, metabolized by the colonic epithelium
- Propionates metabolized by the liver
- and acetates metabolized through the action of muscle tissue

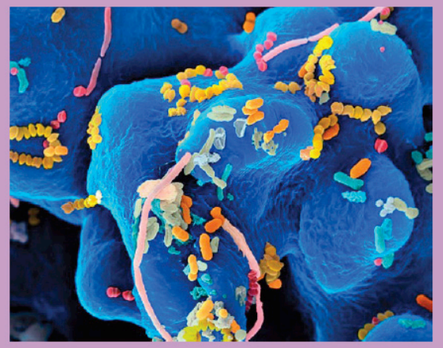
Intestinal bacteria also play a role in synthesizing vitamin B and vitamin K as well as metabolizing bile acids, sterols and xenobiotics. Xenobiotics are typically a synthetic chemical that is foreign to the body or in some cases to an entire ecological system. Xenobiotics are intestinal janitors.

The human body carries about 100 trillion microorganisms in its intestines, a number ten times greater than the total number of human cells in the body. The metabolic activities performed by these bacteria resemble those of an actual organ like a heart or a lung, leading some to liken gut bacteria to a "forgotten" organ. It's estimated that these gut flora have around a hundred times as many genes in aggregate as there are in the human genome.

Our microbiota so very obviously play a large, significant and unquestionably necessary part in good human health and a part we still know vert, very little about.

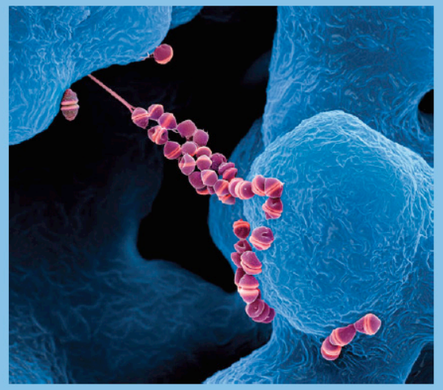
As a species we human beings are rapidly developing a new genera of innumerable and often times rare disorders manifesting with such intrusive and unimaginably odd neurological symptoms such that it's a wonder all approximately 305 million of us aren't already on the verge of a completely and swiftly disabling disorder.

Salmonella are bacteria that can live in the intestinal tracts of humans and other animals. Shown here is a color-enhanced and highly magnified view of Salmonella typhimurium (in red) invading cultured human cells in a great photo from Rocky Mountain Laboratories.



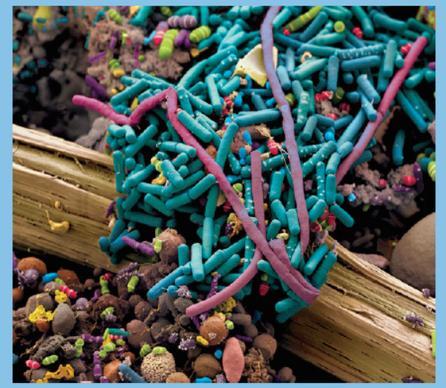
MOUTH MICROBES

The human mouth hosts a panoply of microbes, some taking up residence on the mouth lining (blue) within days after birth. Harmful species form biofilms, like the plaque that encourages tooth decay, or colonize the crevices between teeth and gums, causing periodontal disease. Oral probiotics designed to boost the population of species that outcompete pathogenic ones could help prevent or reverse dental disease. Researchers (very patient researchers) have painstakingly harvested all the plaque from every surface of every tooth. It weighs, on average, about 10 mg. But the teeth only comprise 1/20 of all the oral surfaces. You have to multiply the 10 mg from the teeth by 20 to get the total biomass including cheeks, tongue, etc. We also know that 1 mg of oral biomass typically contains about 100 million microbes. By multiplying the number of microbes in 1 mg by 20, we get the total number of microbes in the entire oral cavity. 100 million microbes x 20 mg biomass = 20 billion oral microbes living in your mouth right now. almost all of those billions of microbes that we swallow began their lives in an oral biofilm. Thus, despite only having (at any given time) 20 billion microbes in our mouths, we nevertheless swallow 100 billion! Five times more than we have. So, those 20 billion microbes in our mouths must be producing and shedding 100 billion additional microbes every day. That's five times their original number. Said another way, they are doubling their numbers five times every 24 hours. Dividing 24 hours by 5 = 4.8 hours, the amount of time it takes for the microbes in our mouths to double their number. There are 20 billion bacteria in your mouth and they reproduce every five hours. If you go 24 hours without brushing, those 20 billion become 100 billion!



STREPTOCOCCUS

A colorized electron microscope image captures delicate chains of streptococcus in a laboratory sample. Though some strep infections can be deadly, many strains are harmless—among the thousands of benign beings that make their home in our bodies. Most Streptococcus genomes are 1.8 to 2.3 Mb in size and encode 1,700 to 2,300 proteins. There are two types of Strep: group A and group B. Group A strep causes Strep throat - a sore, red throat, sometimes with white spots on the tonsils; Scarlet fever - an illness that follows strep throat. It causes a red rash on the body; Impetigo - a skin infection; Toxic shock syndrome; Cellulitis and necrotizing fasciitis (flesh-eating disease). Group B strep can cause blood infections, pneumonia and meningitis in newborns. A screening test during pregnancy can tell if you have it. If you do, I.V. antibiotics during labor can save your baby's life. Adults can also get group B strep infections, especially if they are elderly or already have health problems. Strep B bacteria can cause urinary tract infections, blood infections, skin infections and pneumonia in adults.

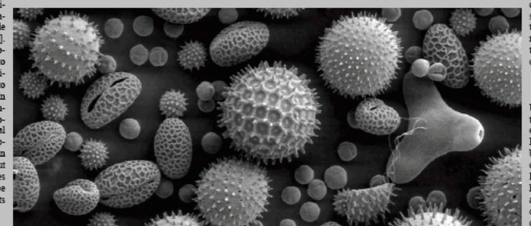


HELICOBACTER

Helicobacter pylori (yellow), a common bacterium that lives in the stomach lining, increases the risk of stomach cancer (brown cells) and peptic ulcers. But over time H. pylori can reduce stomach acid and acid reflux, which may help fend off esophageal cancer. The microbe also appears to help protect us from allergies and asthma. Some scientists suspect that the dramatic increase in those conditions in the industrialized world could be related to the decreasing frequency of H. pylori in our stomachs, which is partly due to high doses of antibiotics in childhood. Helicobacter pylori is a Gram-negative, microaerophilic bacterium found in the stomach, and may be present in other parts of the body, such as the eye. It was identified in 1982 by Australian scientists Barry Marshall and Robin Warren with further research led by British scientist Stewart Goodwin, who found that it was present in patients with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause. It is also linked to the development of duodenal ulcers and stomach cancer. However, over 80% of individuals infected with the bacterium are asymptomatic and it may play an important role in the natural stomach ecology.

metabolism is poorly understood but appears to involve transport to the liver by the portal circulation. It is believed that SCFAs also impact water absorption, local blood flow, and epithelial proliferation in the large intestine [9].

Genomic analysis of gut bacteria offers vivid examples of the role of microbes in nutrient utilization. For example, in 2003, Xu, et al. published the complete genome sequence of the gram-negative anaerobe Bacteroides thetaiotaomicron, a prominent member of the normal intestinal microbiota [10]. Annotation and analysis of the genome revealed a sophisticated apparatus for acquiring and digesting otherwise unusable dietary polysaccharides. This apparatus, including a complex, multi-component, multi-enzyme complex starch utilization system (SUS), consists of over 230 glycoside hydrolase and 15 polysaccharide lyase genes [15]. The genomic analysis demonstrated that B. thetaiotaomicron has evolved the remarkable capacity to sense the availability of carbohydrates in its microenvironment, and that it also has the ability to forage and utilize host-derived glycans (e.g., mucin and heparin). Mechanistic studies in gnotobiotic animals further demonstrated that, when B. thetaiotaomicron senses a scarcity of fucose in the intestinal lumen, it actually induces the gut epithelium to up-regulate expression of fucosylated glycans that can be used by the bacteria as an energy source without harming the host [16]. This body of work illustrates how the remarkable host-microbe synbiosis can be teased apart by pairing genomic sequencing efforts with creative in vivo laboratory studies.



Microbiota and protein metabolism

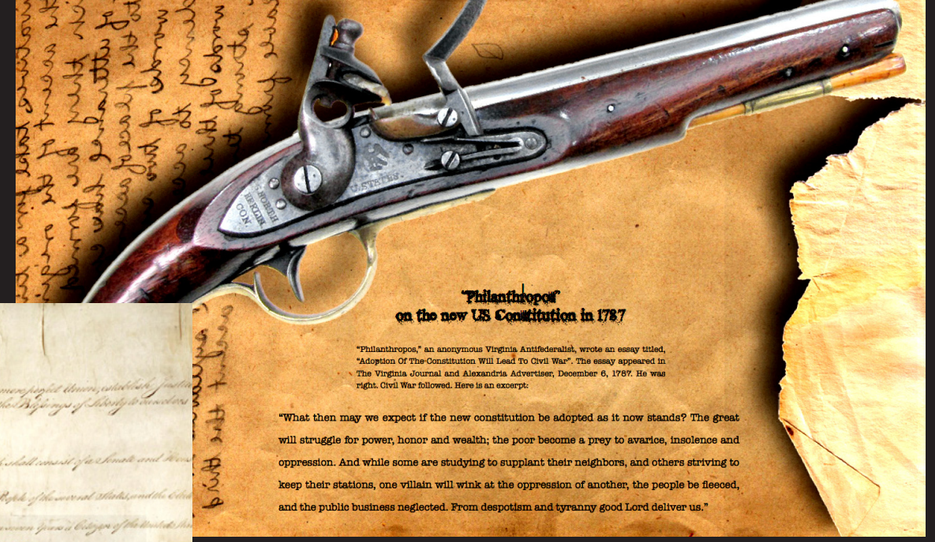
amino acids. More work is needed to define these contributions in both healthy and undernourished humans. The intestinal microbiota also contributes to nitrogen balance by participating in urea nitrogen salvaging (UNS) [21, 22]. Elevated urease expression in gut microbes results in metabolism of urea in the GI tract into ammonia and carbon dioxide. Some of the ammonia can be utilized for microbial synthesis of amino acids. Perhaps more importantly, the nitrogen generated during this process (urea nitrogen) can re-enter the host circulation and serve as a substrate for synthetic processes [23]. Interestingly, reduced urea recycling has been reported in GF animals [24] and in humans receiving antibiotic therapy [25]. Furthermore, several reports indicate that regulation of UNS is important in settings of low N intake and high N demand (e.g., during pregnancy and during periods of rapid somatic growth in infancy) [26–28]. While still relatively preliminary, these studies underscore the relationship between gut microbes and protein metabolism that will likely be further described through on-going characterization of the human microbiome.

MICROBIOTA AND LIPID METABOLISM

Until recently, few studies of the association between lipid metabolism and the microbiome existed. However, important research by Jeffrey Gordon, Fredrick Backhed, and colleagues suggests that the body's supply of triglycerides, a prominent source of energy during critical illness [29], is tightly linked to the intestinal microbiota. These findings have enormous potential relevance for research in a wide range of disease states, including metabolic disorders such as obesity (see below) and cardiovascular disease.

Opinions of the US Constitution in 1787

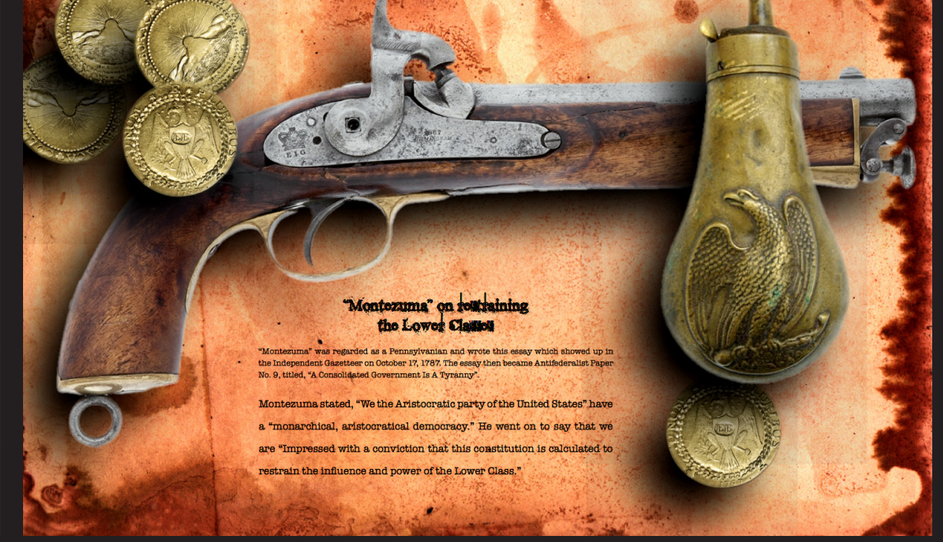
A Back To Reality
Feature Length
Commercial Free
Adventure Story
by Jeff Prager



"Philanthropos" on the new US Constitution in 1787

"Philanthropos," an anonymous Virginia Antifederalist, wrote an essay titled, "Adoption Of The Constitution Will Lead To Civil War". The essay appeared in The Virginia Journal and Alexandria Advertiser, December 6, 1787. He was right. Civil War followed. Here is an excerpt:

"What then may we expect if the new constitution be adopted as it now stands? The great will struggle for power, honor and wealth; the poor become a prey to avarice, insolence and oppression. And while some are studying to supplant their neighbors, and others striving to keep their stations, one villain will wink at the oppression of another, the people be fleeced, and the public business neglected. From despotism and tyranny good Lord deliver us."



"Montezuma" on restraining the Lower Classes

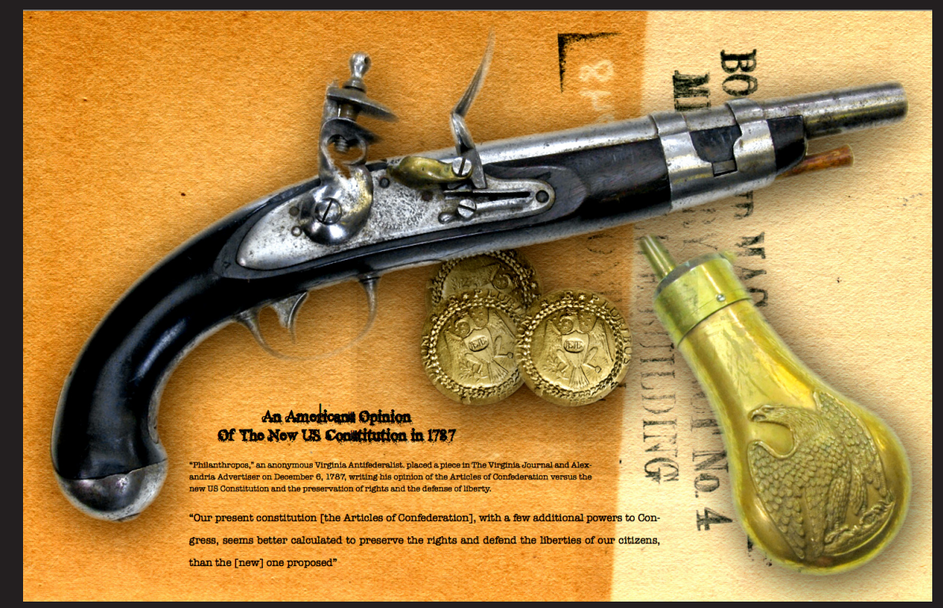
"Montezuma" was regarded as a Pennsylvanian and wrote this essay which showed up in the Independent Gazetteer on October 17, 1787. The essay then became Antifederalist Paper No. 9, titled, "A Consolidated Government Is A Tyranny".

Montezuma stated, "We the Aristocratic party of the United States" have a "monarchical, aristocratical democracy." He went on to say that we are "Impressed with a conviction that this constitution is calculated to restrain the influence and power of the Lower Class."

An opinion from a speech by Patrick Henry in 1788

The following excerpt is from a speech by Patrick Henry on June 5th, 1788 at the Virginia Ratifying Convention. It was published as Anti-Federalist Paper No. 4 titled, "Foreign Wars, Civil Wars, and Indian Wars - Three Bugbears". This excerpt of the commentary by Henry refers to the new US CONstitution and was a warning, even as far back as 1788, that "the people" were in serious trouble.

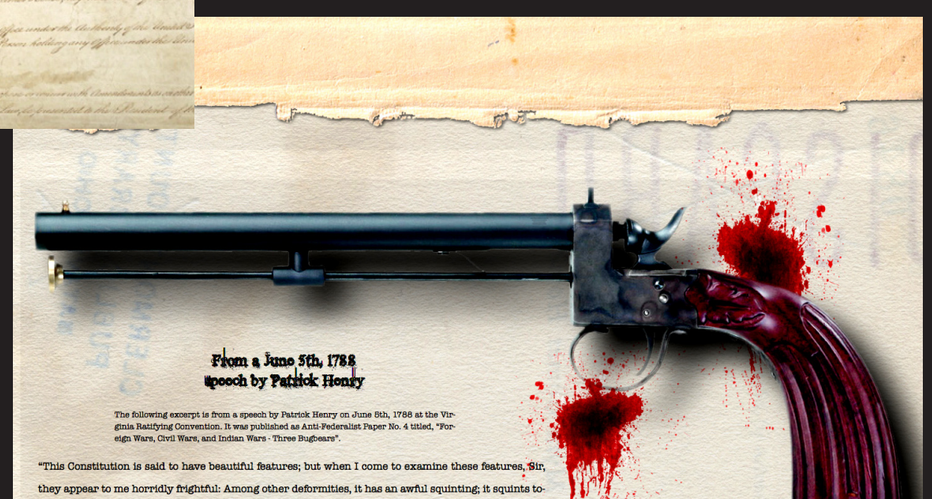
"We are cautioned by the honorable gentleman, who presides, against faction and turbulence. I acknowledge that licentiousness is dangerous, and that it ought to be provided against: I acknowledge, also, the new form of government may effectually prevent it: yet there is another thing it will as effectually do — it will oppress and ruin the people."



An American Opinion Of The New US Constitution in 1787

"Philanthropos," an anonymous Virginia Antifederalist, placed a piece in The Virginia Journal and Alexandria Advertiser on December 6, 1787, writing his opinion of the Articles of Confederation versus the new US Constitution and the preservation of rights and the defense of liberty.

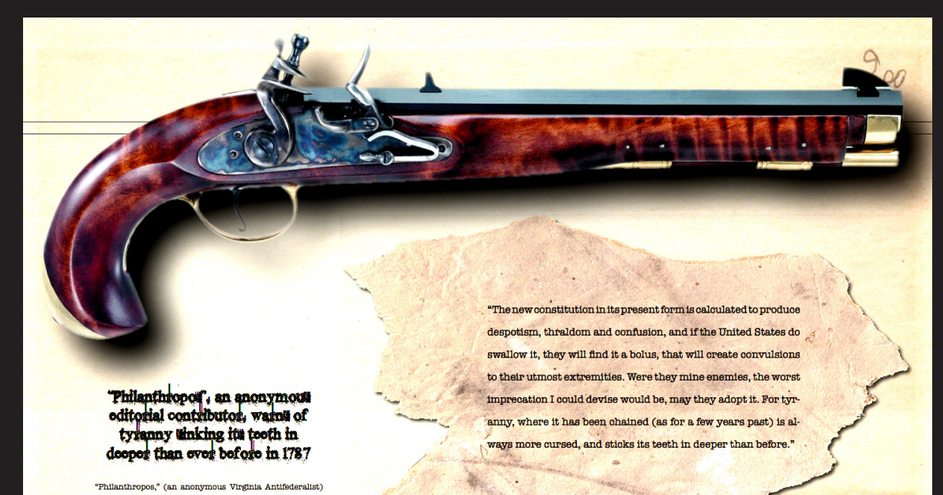
"Our present constitution [the Articles of Confederation], with a few additional powers to Congress, seems better calculated to preserve the rights and defend the liberties of our citizens, than the [new] one proposed"



From a June 5th, 1788 speech by Patrick Henry

The following excerpt is from a speech by Patrick Henry on June 5th, 1788 at the Virginia Ratifying Convention. It was published as Anti-Federalist Paper No. 4 titled, "Foreign Wars, Civil Wars, and Indian Wars - Three Bugbears".

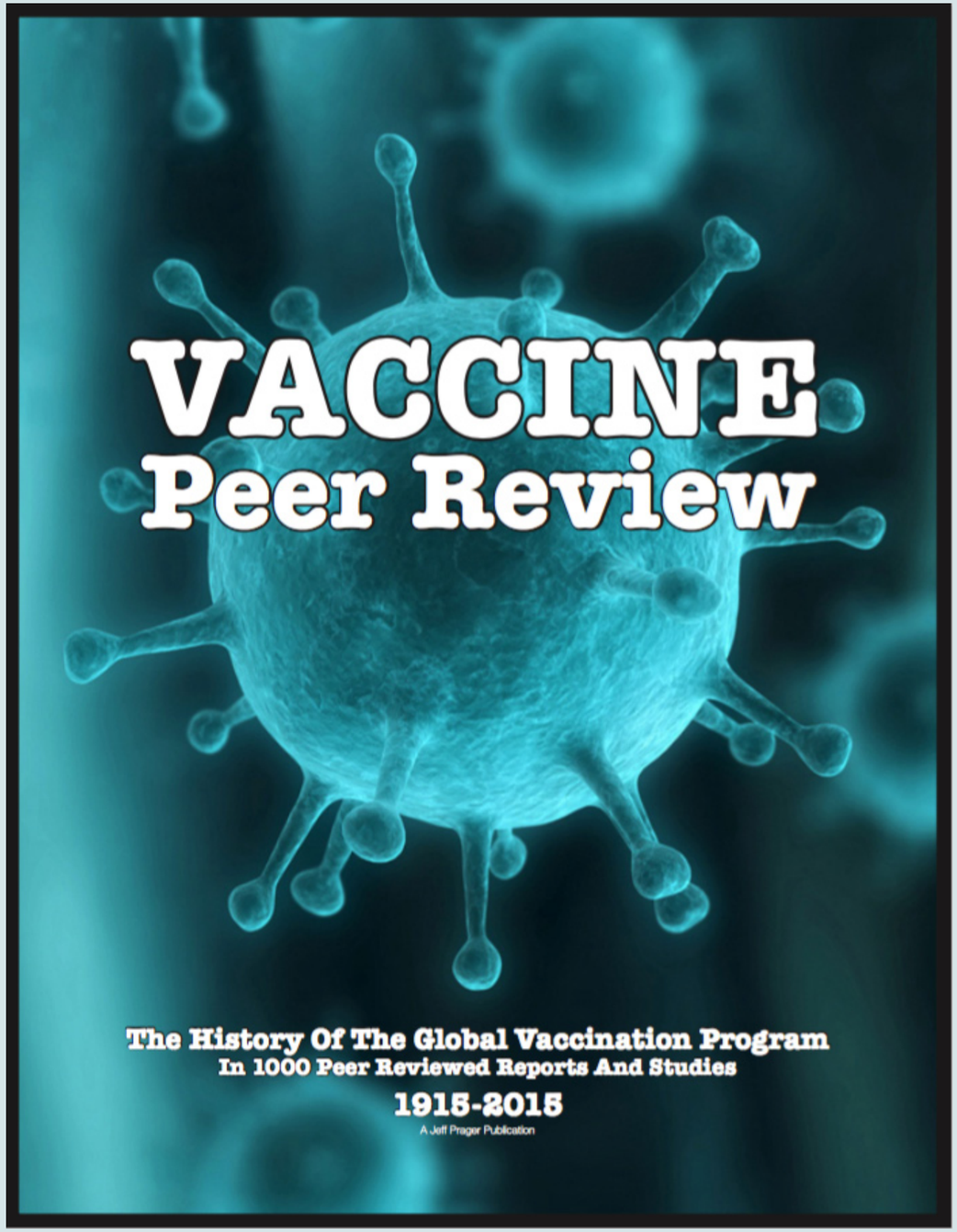
"This Constitution is said to have beautiful features; but when I come to examine these features, Sir, they appear to me horridly frightful: Among other deformities, it has an awful squinting; it squints to-



"Philanthropos", an anonymous editorial contributor, warns of tyranny sinking its teeth in deeper than ever before in 1787

"Philanthropos," (an anonymous Virginia Antifederalist) made the comment at right which appeared in The Virginia Journal and Alexandria Advertiser on December 6, 1787.

"The new constitution in its present form is calculated to produce despotism, thraldom and confusion, and if the United States do swallow it, they will find it a bolus, that will create convulsions to their utmost extremities. Were they mine enemies, the worst imprecation I could devise would be, may they adopt it. For tyranny, where it has been chained (as for a few years past) is always more cursed, and sticks its teeth in deeper than before."



"There is a great deal of evidence to prove that immunization of children does more harm than good"

Dr. J. Anthony Morris, former Chief Vaccine Control Officer, FDA

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Autoimmune Syndromes and Inflammatory Syndromes

Caused By Adjuvants In Vaccines

Also Known As

ASIA

A Two Smoking Guns Publication
Produced by Jeff Prager

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Renegade Publishing

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Just Say 'No' To Food Drugs